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Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Support: Campbell Foundation Research Grant Program
Office of Undergraduate Research Grand Valley State University

Title: Cyclic AMP dependent protein kinase regulation of Nato3 induction of dopamine neuron gene expression

Authors: M. OKROS[1], M. FRANTZESKAKIS[2], P. CHOWDHARY[1], *M. K. DELANO-TAYLOR[3];
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Abstract: Nato3 has been shown to be necessary for normal dopamine neurogenesis *in vivo* but it is not known if Nato3 is sufficient to drive dopamine neurogenesis. Others have shown Nato3 can induce *Sonic hedgehog* and *Nurr1* mRNA expression in the immortalized mouse midbrain cell line SN4741. However it is not known if other factors such as phosphorylation may regulate the magnitude or number of dopaminergic genes induced by Nato3. In this study we test if the presence of the catalytic subunit of cAMP dependent protein kinase can promote the effect of Nato3 expression of dopaminergic genes.

Disclosures: M. Okros: None. **M. Frantzeskakis:** None. **P. Chowdhary:** None. **M.K. Delano-Taylor:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant DE024783

Title: Gene regulatory interactions governing cranial neural crest cell differentiation along neurogenic and chondrogenic lineages

Authors: *M. R. REPLOGLE[1], A. RAU[3], P. L. AUER[2], A. J. UDVADIA[1];
[1]Biol. Sci., [2]Joseph J Zilber Sch. of Publ. Hlth., Univ. of Wisconsin - Milwaukee, Milwaukee, WI; [3]Animal Genet. and Integrative Biol., Inst. Natl. de la Recherche Agronomique, Jouy-en-Josas, France

Abstract: Disruption of cranial neural crest (CNC) development can result in a broad spectrum of congenital malformations, many of which are often associated with pediatric syndromes. As developmental precursors, CNC cells are known to give rise to a diverse array of ectodermal and mesoectodermal cell types, from neurons and glia of the peripheral nervous system to the cartilage and bone of the face. However, we currently have a limited understanding of the molecular programming underlying CNC differentiation along ectodermal versus mesoectodermal cell lineages. Recently, we established a murine culture system modeling CNC cell differentiation along the neurogenic and chondrogenic lineages. Systematic characterization of the cultured cells identified reproducible timelines for changes in cell shape, protein expression and aggregation behavior that mimic the progression of neurogenic and chondrogenic differentiation *in vivo*. Using this culture system, we are assessing global changes in transcription and chromatin accessibility that accompany CNC cells as they transition to (1) intermediate progenitors, and then (2) differentiated peripheral neurons or cartilage matrix-producing chondrocytes. Integration of the information gathered will provide a detailed roadmap of changes in gene expression during CNC cell differentiation and the unique lineage-specific regulatory interactions that drive cell fate acquisition in a stepwise and time-sensitive manner. Together, these analyses will allow further investigation into the hierarchical, cell-intrinsic circuitry contributing to the plasticity and developmental potential of the CNC. Moreover, elucidation of the gene regulatory networks governing CNC cell differentiation provides a platform for discovering the molecular targets of genetic and environmental factors that lead to CNC-related birth defects and disorders.

Disclosures: M.R. Replogle: None. **P.L. Auer:** None. **A.J. Udvadia:** None. **A. Rau:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: Wellcome Trust Grant 03714MA
NIH Grant NS095654
NIH Grant MH106934

Title: Single-cell transcriptomics reveals early emergence of cortical interneuron diversity in the mouse embryo

Authors: *D. MI[1], Z. LI[2], L. LIM[1], M. LI[2], M. MOISSIDIS[1], Y. YANG[3], T. GAO[2], D. PRICE[3], T. PRATT[3], N. SESTAN[2], O. MARIN[1];
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Abstract: The cerebral cortex is the seat of higher-order brain functions. It consists of a multitude of specialized, precisely positioned and interconnected cell types that assemble into specialized neuronal circuits to execute complex behaviors. One major goal of neuroscience is to understand how small pool of neural progenitor cells generate the vast diversity of neuronal cell types during cortical development. The cerebral cortex contains a heterogeneous collection of GABAergic interneurons with unique morphological, electrophysiological and molecular characteristics, but the mechanisms generating interneuron diversity remain controversial. One model proposes that interneuron identity is specified at the level of progenitors or shortly after becoming postmitotic; the competing model postulates that interneuron identity is established relatively late, through interactions with the cortical environment. Here we use single-cell transcriptomics to study the origins of cortical interneuron diversity in mouse. We identify distinct types of progenitor cells and newborn neurons in the ganglionic eminences, the embryonic proliferative regions that give rise to cortical interneurons. These embryonic precursors show temporally and spatially restricted transcriptional patterns that lead to different classes of interneurons in the adult cerebral cortex. Our findings suggest that shortly after the interneurons become postmitotic, their diversity is already patent in their diverse transcriptional programs which subsequently guide further differentiation in the developing cortex.

Disclosures: D. Mi: None. **Z. Li:** None. **L. Lim:** None. **M. Li:** None. **M. Moissidis:** None. **Y. Yang:** None. **T. Gao:** None. **D. Price:** None. **T. Pratt:** None. **N. Sestan:** None. **O. Marin:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH-5T32EB005582-13

Title: Transcriptomically defined neuronal subtype specification in the type-II neuroblast lineages of *Drosophila melanogaster*

Authors: *N. S. MICHKI[1], Y. LI[2], K. SANJASAZ[3], C.-Y. LEE[2,4], D. CAI[2,5,1];
[1]Biophysics, [2]Cell and Developmental Biol., [3]Moleclular, Cellular, and Developmental Biol., [4]Life Sci. Inst., [5]Neurosci., Univ. of Michigan, Ann Arbor, MI

Abstract: The expansive neural diversity observed in vertebrates requires efficient and robust subtype specification mechanisms. However, the scale of neurogenesis in even simple vertebrates has made studying these mechanisms particularly challenging. The 16 type-II neural stem cells (neuroblasts) in *Drosophila melanogaster* (the fruit fly) provide an excellent *in vivo* model system for probing the mechanisms behind neural subtype specification, as the intermediate neural progenitors (INPs) they generate are remarkably similar to the neural progenitors found in lower vertebrates and humans [Hansen et al., Nature, 2010]. We aim to better understand both *which* neural fates are specified during type-II neurodevelopment and *how* they are specified by their progenitors. Using genetic targeting to fluorescently label and sort the type-II neuroblasts' progenies, we acquired scRNA-seq data from ~3800 fluorescently sorted cells and used standard bioinformatics pipelines to identify a variety of different cell type clusters representing putative progenitor (INP), precursor (GMC), neuronal, and glial subtypes. The presence of clusters clearly expressing previously identified type-II system markers, such as *Dichaete*, *grainy-head*, *eyeless*, *bsh*, and *toy* [Bayraktar and Doe, Nature, 2013], give us confidence that our cell population is pure. Guided by this and the many other prior studies of the type-II system, we manually identified known and new subtype clusters and performed differential gene expression analysis to identify a variety of new marker genes that may also play a role in specifying final cell fates. Using gene-reporter fusion constructs and immunostaining, we show that these genes are in fact upregulated in a subset of the type-II progenies. By performing RNAi knock-down experiments, we hope to determine which, if any, are necessary for correctly carrying out the stereotypical INP temporal transcription factor progression. These critical insights will enable us to better understand both the scale of and mechanisms underlying neuronal subtype specification in the type-II neuroblasts and, due to their similarity to vertebrate neural stem cells, may further our understanding of why neurogenesis via intermediate progenitors is the predominant form of neurogenesis in vertebrates.

Disclosures: **N.S. Michki:** None. **Y. Li:** None. **K. Sanjasaz:** None. **C. Lee:** None. **D. Cai:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

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Topic: A.01. Neurogenesis and Gliogenesis

Support: Grants- in-Aid for Scientific Research (Grant 15H04268 to M.H.)

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Naito Foundation
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Uehara Foundation

Title: Notch signaling in the cerebellar granule cell development

Authors: T. ADACHI[1,2], S. MIYASHITA[1], M. YAMASHITA[1,3], R. D. SHIRAISHI[1,3], M. M. SHIMODA[1,2], T. OWA[1], M. HOSHINO[1];
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Abstract: The development of the mammalian nervous system is controlled by a variety of extracellular signals at the timing of cell division, differentiation and migration to proper locations. Cerebellar granule cell progenitors (GCPs) are produced in the Rhombic lip, migrate along the surface of the cerebellar primordium to form the external granule layer (EGL), and exit cell cycle to differentiate into granule cells (GCs). It is known that GCP proliferation and GC differentiation are controlled by extracellular stimuli such as WNT, SHH, and BMP during their development. However, the function of Notch signaling in the granule cell development is poorly understood, despite the numerous previous studies for this pathway in the development of varous tissues in vertebrates and invertebrates. In this study, we investigated the expression profiles of Notch singaling molecules in GCPs and GCs during cerebellar development. Then we introduced overexpression/knockdown vectors for various Nocth-signaling molecules into the EGL by *in vivo* electroporation to investigate their roles in granule cell development. Overexpression and knockdown for some molecules obviously affected proliferation and differentiation of GCPs/GCs, suggesting that Notch signaling regulates the development of cerebellar granule cells.

Disclosures: T. Adachi: None. **S. Miyashita:** None. **M. Yamashita:** None. **R.D. Shiraishi:** None. **M.M. Shimoda:** None. **T. Owa:** None. **M. Hoshino:** None.

Poster

457. Mechanisms of Cell Fate

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Program #/Poster #: 457.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant AG045781

Title: Differential regulation of neocortical and hippocampal astrogliogenesis by neogenin

Authors: *D. SUN, W. XIONG;
Case Western Reserve Univ., Cleveland, OH

Abstract: Astrocytes, a major type of glial cells in the brain, play important roles in modulating synaptic transmission and information processing, and maintaining CNS homeostasis. The abnormal astrocytic differentiation contributes to dysfunctions of synaptic plasticity and neuropsychological disorders. Thus, it is of considerable interest to investigate how astrogliogenesis is regulated. Neogenin, a member of deleted in colorectal cancer (DCC) family receptors, appears to play important roles in regulating cortical astrogliogenesis. Neogenin is highly expressed in neural stem cells (NSCs) and astrocytes. Knocking out (KO) Neogenin in NSCs as well as in adult astrocytes selectively reduced neocortical astrocytes, which are likely due to impaired BMP-induced cortical astrogliogenesis and decreased astrocyte self-renewal. Further mechanical studies suggest that neogenin in NSCs is required for BMP2 activation of YAP, a crucial transcriptional factor for cortical astrocytic differentiation. Interestingly, neogenin in NSCs is only required for cortical, but not hippocampal, astrogliogeneis, and in hippocampus, neogenin in NSCs is necessary for adult dentate gyrus neurogenesis. The latter function appears to be due to neogenin regulation of Gli1, a transcriptional factor downstream of sonic hedgehog (Shh) pathway. Taken together, these results demonstrate a differential regulation of cortical and hippocampal astrogliogenesis by neogenin, and implicate neogenin as a co-receptor for BMP or Shh in a brain region dependent manner.

Disclosures: D. Sun: None. **W. Xiong:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R01 EY015290
Simons Foundation Senior Fellow Award

Title: Neurogenesis of retinal ganglion cells in the pigmented and albino retina

Authors: *N. SLAVI, R. L. OAKS-LEAF, S. KHALID, C. MASON;
Mortimer B. Zuckerman Mind Brain Behavior Inst., Columbia Univ., New York, NY

Abstract: Proper binocular vision in higher vertebrates depends on specific proportions of retinal ganglion cells (RGCs) projecting to the same (ipsilateral) or opposite (contralateral) side of the brain. In albinism, the ipsilateral retinogeniculate projection is diminished, and the

contralateral projection is increased, leading to impaired stereo vision. To understand the long-standing enigma of how the lack of melanin in the retinal pigment epithelium (RPE) relates to aberrations in the circuitry from the eye to brain in albinism, we are investigating the events that govern early neural retinal development in pigmented and albino (tyrosinase mutants; $Tyr^{c\text{-}2J}$) C57BL/6J mice. Besides the neural retina itself, the ciliary margin zone (CMZ) at the distal-most tip of the embryonic retina was recently described as a niche for RGC neurogenesis. The cell cycle regulator Cyclin D2 and the transcription factor Msx1 are enriched in the ventral CMZ and are associated with neurogenesis and control of cell fate. We quantified the apical vs basal, and peripheral vs central distribution of Msx1- and Cyclin D2-expressing cells, to create a detailed spatiotemporal atlas of progenitors in the CMZ over time. We found that during embryonic retinal development, Cyclin D2 expression is altered in the albino compared to pigmented CMZ. In addition, using birthdating techniques, we probed for differences in the rates of cell proliferation and cell cycle exit within the CMZ. We are also performing fate mapping studies to characterize the generation and identity of cells originating from the CMZ. This study will elucidate how RGC neurogenesis is controlled in the normal visual system, and provide information on the underpinnings of perturbed retinogeniculate connectivity leading to visual syndromes such as albinism.

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Poster

457. Mechanisms of Cell Fate

Location: Hall A

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Program #/Poster #: 457.08/A8

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R37 NS096359
NIH Grant R01 NS075243

Title: Single cell transcriptomics resolves intermediate glial progenitors and uncovers pivotal determinants of cell fate and gliomagenesis

Authors: *J. WANG[1,2], J. WANG[1,2], Q. WENG[2], D. HE[1], Z. CHENG[3], F. ZHANG[1], S. S. POTTER[1], G. YU[3], Q. R. LU[1];
[1]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [2]Zhejiang Univ., Hangzhou, China; [3]Virginia Polytechnic Inst. and State Univ., Arlington, VA

Abstract: Abnormal development of glial progenitors, including astrocyte lineage precursors and oligodendrocyte precursor cells (OPCs), contributes to tumorigenesis and various neurological diseases. Although single-cell analysis of human glioma tissues has been reported, the tumorigenic cell of origin and the molecular links between native glial progenitors and pre-

cancerous or neoplastic cells during glioma transformation have not been fully defined. By using single-cell RNA sequencing (scRNA-seq) on prospective astrocyte lineage cells and OPC populations from neonatal mouse cortices, we uncovered an unanticipated diversity of glial progenitor pools with unique molecular identities in developing brain. We found that astrocyte lineage cells are much more dynamic than previously appreciated in the developing cortex and uncovered an intermediate glial progenitor cell population (iGCs), which express the markers of both astrocytic signature genes and oligodendrocyte lineage genes during astrocyte lineage development. In contrast to the astrocyte lineage, the progenitors of oligodendrocytes exhibited a fate-restricted continuum in the lineage, encompassing a primitive OPC intermediate (pri-OPCs) prior to OPC commitment. Application of scRNA-seq to a murine model of GBM revealed that primitive OPC intermediates disproportionately contributed to glioma formation. Analyses of different tumorigenic phases showed that reprogramming of the OPC intermediates into a stem-like state, rather than direct stem-cell proliferation, resulted in their malignant transformation. Similar actively cycling pri-OPC intermediates were prominent components in different human gliomas caused by distinct driver mutations. Moreover, we established a machine-learning algorithm to identify glial lineage-driving networks and discovered an RNA-binding protein, Zfp36l1 as a critical regulator for both glial fate specification and glioma growth. Together, our results resolve the dynamic repertoire of common and divergent glial progenitors during development and tumorigenesis and indicate a conserved regulatory network underlying brain development and tumorigenesis.

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Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

Support: MH101188
NS109379

Title: Temporal, regional, and functional intersection of microglia, precursor cells, and vasculature in developing cerebral cortex

Authors: E. PENNA, *S. C. NOCTOR;
MIND Inst., UC Davis, Sacramento, CA

Abstract: Formation of the cerebral cortex begins during gestation with the establishment of fundamental building blocks that include neural precursor cells. Precursor cells that line the

lateral ventricles produce the vast majority of cortical neurons and glia that populate mature neocortex. Evidence gathered to date reinforces the concept that precursor cells function within a complex milieu comprising multiple cell types. Our published work showed that microglial cells are present in the proliferative zone cells during cortical neurogenesis; that microglia make extensive contact with the soma and processes of precursor cells that undergo division at the margin of the lateral ventricle; and that microglia also phagocytose neural and glial precursor cells during peak stages of cell genesis. Published evidence also shows that endothelial cells influence the function of neural precursor cells, and that precursor cells are often located near blood vessels. We have shown that microglia also associate with vasculature in the developing neocortex for reasons not yet clear. Microglia derive from precursor cells in the yolk sac and enter the cerebral cortex during prenatal stages of cell genesis. Previous work proposed that microglia seeding the cerebral cortex travel along vasculature as a means of entry to the cortical parenchyma. To investigate the temporal, regional and functional relationships between precursor cells, microglia, and vasculature in the developing cerebral cortex, we completed a developmental study of microglial colonization examined in the context of vascular development and precursor cell distribution. Our findings demonstrate that microglia contribute to the complex environment in which mitotic precursor cells, neuronal and glial progeny, and blood vessels are embedded in the cortical proliferative zones. The most relevant implication of these results is that cortical histogenesis proceeds from an appropriate interplay between multiple systems. Furthermore, factors that impinge on any single component may put development of the cerebral cortex at risk, and altering the development of a single component could change the timing and trajectory of cortical development and increase susceptibility for altered neurodevelopmental outcomes.

Disclosures: E. Penna: None. **S.C. Noctor:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIMH Grant P50 MH103222

Title: RNAi inhibition of KAT II during postnatal development alters cell generation in the subventricular zone and oliodendrogenesis in the corpus callosum

Authors: *S. M. CLARK[1], T.-C. MOU[1], A. LANIYAN[1], R. CHANDRA[2], L. H. TONELLI[1]; [1]Psychiatry, [2]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Kynurenine/alpha-aminoadipate aminotransferase (AADAT/KAT II), has been extensively studied for its role in the catabolism of tryptophan and the conversion of kynurenine into kynurenic acid, a metabolite with glutamatergic and cholinergic modulatory activity. We have previously reported that KAT II is expressed in astrocytes found in the proliferative zones of the adult rat brain: the subventricular zone (SVZ) of the lateral ventricles, which shows the highest expression, and the subgranular zone of the dentate gyrus in the hippocampus. In the present study we examined KAT II mRNA expression during rat brain development from embryonic day 15 through adolescence. Consistent with prior reports on KAT II catabolic activity, mRNA for this enzyme was not detectable in the embryonic brain; however, by postnatal day (PND) 7 KAT II expression was evident in the SVZ, whence expression spread to the corpus callosum (by PND 14) and hippocampus (PND 21), reaching stable levels by PND 28. Interestingly, KAT II expression regionally and temporally parallels myelination during postnatal development. Hence, we hypothesized that KAT II may play a role in cell proliferation and white matter development in the postnatal brain. To test this, we administered AAV-shRNAi targeted against KAT II to Wistar rat pups on PND 7 via intranasal inoculation followed by daily injections of 5' Bromo-2' deoxyuridine (BrdU; 100 mg/kg, i.p.) for one week starting on PND 14. BrdU incorporation and the generation of oligodendrocytes were assessed 3 weeks later (PND 42). Examination of the SVZ revealed a significant increase in BrdU+ cells in animals treated with shRNAi. Nevertheless, there were fewer BrdU+ cells in the corpus callosum and a reduction in the number of Olig2+ cells. Analysis of Ki67 in the corpus callosum also showed a significant reduction in the number of cells in the cell cycle. These findings support a role for KAT II in oligodendrogenesis during postnatal development, specifically in the proliferation and migration of precursor cells to the corpus callosum. While additional studies are required, these results suggest that perturbation of this system during postnatal development could result in long term effects on white matter integrity and function.

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Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.11/A11

Topic: A.01. Neurogenesis and Gliogenesis

Support: NICHD Division of Intramural Research Program

Title: Integration of single cell transcriptomes and chromatin profiles to detect regulatory elements critical to interneuron development

Authors: *C. RHODES, D. LEE, Y. ZHANG, T. PETROS;
NIH, Bethesda, MD

Abstract: Mitotic progenitors in the ventricular/subventricular zones (VZ/SVZ) of the dorsal and ventral forebrain display similar cell cycle and neurogenic dynamics. Yet the dorsal telencephalon gives rise to glutamatergic excitatory cells whereas GABAergic inhibitory interneurons arise from three ganglionic eminences in the ventral telencephalon (MGE, LGE and CGE). GABAergic interneurons are an incredibly diverse cell population that perform critical roles in neural network function. Despite substantial evidence that initial interneuron subgroup fate is specified within the GEs, very few fate determining genes have been identified. One possibility is that interneuron progenitors contain epigenetic signatures biasing cells towards a particular interneuron fate that are not yet apparent in the transcriptome. Transcription of a gene is highly dependent upon chromatin modifications at enhancers and promoters, but we lack a comprehensive understanding of how such non-coding genomic regions influence cell fate during embryogenesis.
In this study, we perform single cell assay transposase-accessible chromatin (scATAC-Seq), in combination with single cell RNA (scRNA-Seq) sequencing to characterize the relationship between chromatin modifications and gene expression in progenitors from the dorsal and ventral telencephalon. Our initial analysis detects significant differences in chromatin accessibility within cis-regulatory elements of developmentally critical genes between brain regions. By examining chromatin profiles of lineage-specific genes across cell types, we can detect putative enhancers associated with interneuron fate determination. Experiments are ongoing to assess the functional role of candidate enhancer-gene interactions in regulating interneuron fate determination. These insights increase our knowledge of fate determining mechanisms and could open new avenues for understanding how disease-associated genes could perturb interneuron fate and maturation.

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Poster

457. Mechanisms of Cell Fate

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Program #/Poster #: 457.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIMH R01 MH049428
NIGMS R35 GM119831

Title: Mapping gene regulatory networks generating cell diversity in the embryonic basal ganglia

Authors: *A. N. RUBIN[1], L. SU-FEHER[2], S. N. SILBERBERG[1], K. J. LIM[1], H. TIAN[1], A. S. NORD[2], J. L. R. RUBENSTEIN[1];
[1]Nina Ireland Lab. of Developmental Neurobio., Univ. of California San Francisco, San Francisco, CA; [2]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA

Abstract: The progenitor domains of the basal ganglia - the medial, caudal and lateral ganglionic eminences (MGE, CGE, LGE) - produce the GABAergic projection neurons that populate the adult striatum, globus pallidus, amygdala and other subpallial structures, as well as interneurons that migrate to pallial (e.g. cortex) and subpallial regions (e.g. striatum). During development, several transcription factors with regionally defined expression patterns within the ganglionic eminences participate in specifying the cell types produced there, including Nkx2-1, Nr2f2 and Otx2. However, efforts to elucidate the complete transcriptional circuitry that generates cell diversity in the basal ganglia have been hampered by the heterogeneity of the ganglionic eminences and their derivatives. We also do not know how early the known cell type specification factors begin to have a role. We aim to use single cell RNA-seq on embryonic day (E)11.5 to probe early transcriptional differences, and to integrate this with epigenomic characterization by histone ChIP-seq and ATAC-seq to elucidate the regulatory elements that are part of the transcriptional networks driving specification at this stage. We hypothesize that transcriptional networks with specific spatial activity drive MGE cell fate decisions to generate neuronal diversity. We have used previously identified, defined activity patterns of regulatory elements to label and purify regionally distinct progenitor domains of the ganglionic eminences, as well as spatially intermixed lineages that have been fate-mapped to distinct populations in the adult. We have identified differentially expressed candidate regulators of early cell fate decisions in the MGE and are assessing their roles in cell type specification. This work contributes to mapping of the transcriptional circuitry driving fine-grained cell fate decisions within the developing basal ganglia.

Disclosures: A.N. Rubin: None. **L. Su-Feher:** None. **S.N. Silberberg:** None. **K.J. Lim:** None. **H. Tian:** None. **A.S. Nord:** None. **J.L.R. Rubenstein:** None.

Poster

457. Mechanisms of Cell Fate

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Topic: A.01. Neurogenesis and Gliogenesis

Support: Canadian NSERC Discovery grant
and NCE NeuroDevNet/KidsBrainHealth Network award

Title: Identification of transcribed enhancers critical for cerebellar development

Authors: *M. RAMIREZ[1], R. ROBERT[3], J. T. YEUNG[2], F. CONSORTIUM[4], D. GOLDOWITZ[5];
[2]Med. Genet., [1]Univ. of British Columbia, Vancouver, BC, Canada; [3]Univ. of Rennes 1, Rennes, France; [4]RIKEN, Yokohama, Japan; [5]Med. Genetics; U of BC, Ctr. for Mol. Med. & Ther., Vancouver, BC, Canada

Abstract: The developing cerebellum requires intricate spatial and temporal expression of genes. The spatiotemporal control of gene expression is partially driven by non-coding regulatory sequences known as enhancers. Bi-directional transcription of non-coding enhancer RNAs (eRNAs) at enhancer sequences has been described as a signal of active enhancers and can be used to identify active enhancer elements during development. The FANTOM5 consortium has defined a catalogue of transcribed mouse enhancers from several mouse tissues, including cerebellum samples from 12 time-points spanning embryonic and postnatal development submitted by our lab. *This study aims to establish a comprehensive atlas of transcribed enhancer elements critical for cerebellar development and characterize the role of transcribed enhancers and their respective eRNAs in brain development.*
We have identified 2359 transcribed enhancers through eRNA expression analysis and validated activity using ChIP-seq of enhancer associated histone marks H3K27ac and H3K4me1. Co-expression analysis between eRNA and expression of genes located in *cis* was conducted to identify correlated predicted gene targets highly enriched for developmental function. Using a specific set of biological criteria, we have identified clusters of transcribed enhancers predicted to regulate genes involved in postnatal granule cell differentiation and maturation. *In situ* hybridization has revealed that expression of eRNAs from these enhancer clusters is spatially identical to the predicted gene target (ex. Nfib), validating our predictive pipeline. We plan to investigate the role of transcribed enhancers and eRNAs in neuron development by perturbing activity using a CRISPR interference system and knocking down their eRNAs in a granule cell culture systems. Validated enhancers will then be knocked out of in the whole mouse the mouse genome for further characterization *in vivo.*

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Poster

457. Mechanisms of Cell Fate

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Program #/Poster #: 457.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH/NINDS (R01NS100471)
KHIDI (grant number: HI17C0447)

Title: Critical roles of ARHGAP36 as a signal transduction mediator of Shh pathway in lateral motor columnar specification

Authors: H. NAM[1], S. JEON[2], S.-K. LEE[2], ***S. LEE**[1];
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Abstract: During spinal cord development, Sonic hedgehog (Shh), secreted from the floor plate, plays an important role in the production of motor neurons by patterning the ventral neural tube, which establishes MN progenitor identity. It remains unknown, however, if Shh signaling plays a role in generating columnar diversity of MNs that connect distinct target muscles. Here, we report that Shh, expressed in postmitotic MNs, is essential for the formation of lateral motor column (LMC) neurons at the brachial level. This novel activity of Shh is mediated by its downstream effector ARHGAP36, whose expression is directly induced by the MN-specific transcription factor complex Isl1-Lhx3. Furthermore, we found that AKT stimulates the Shh activity to induce LMC MNs through the stabilization of ARHGAP36 proteins. Taken together, our data reveal that Shh, secreted from MNs, plays a crucial role in generating MN diversity via a regulatory axis of Shh-AKT-ARHGAP36 in the developing spinal cord.

Disclosures: **H. Nam:** None. **S. Jeon:** None. **S. Lee:** None. **S. Lee:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

Title: Behavioral and thalamic repercussions following the reduction of primary visual area size by cortical Emx2 deletion

Authors: ***C. SCHAFFER**[1], O. AJAYI[1], D. DELBRUNE[1], A. SHASTRI[1], S. AKHIDENOR[1], A. B. ZEMBRZYCKI[2], A. M. STOCKER[1];
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Abstract: The neocortex is unique to mammals and possesses distinct functional areas responsible for processing specialized information. Among these functional areas are the primary sensory areas that process different types of sensory information. Gene expression gradients in the early telencephalon provide positional cues and ultimately play a prominent role in determining the size and location of these functional areas during corticogenesis, a process called area patterning. The transcription factor Emx2 has been found to play a crucial role in this process, and the removal of this gene from the cortex has been shown to result in a significant

shift of primary sensory area location and a decrease in primary visual area (V1) size. Previous research has demonstrated that cortex-specific genetic changes result not only in alterations in primary area size, but also in rearrangements in the corresponding thalamic nucleus. We explored whether the reduction in V1 mediated by a cortex-specific deletion of Emx2 (cKO) resulted in thalamic changes. Our results indicated that the size of the visual thalamic nucleus, dorsal lateral geniculate, did not change in Emx2 cKO mutants that possess a smaller V1. However our results also demonstrated that the thalamic reticular nucleus (TRN) is reduced in size in Emx2 cKOs, despite the lack of genetic manipulation outside of the cortex. Furthermore this reduction in TRN occurred during the critical period, as no changes were observed prior to its onset (postnatal day 18 in mice). We also explored whether these anatomic alterations also had behavioral repercussions. To test for a change in visually-mediated behaviors we employed the looming visual stimulus behavioral paradigm. Behavioral alterations that accompany top-down plasticity driven changes will be further explored and discussed.

Disclosures: C. Schaffer: None. **O. Ajayi:** None. **D. Delbrune:** None. **A. Shastri:** None. **S. Akhidenor:** None. **A.B. Zembrzycki:** None. **A.M. Stocker:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: Ellen R. and Melvin J. Gordon Center for the Cure and Treatment of Paralysis
NIMH Grant R56MH119156
NINDS Grant R01NS102228
Harvard Brain Science Initiative

Title: Diversity and embryonic origin of septal neurons: Analysis of developmental trajectories

Authors: *M. TURRERO GARCIA[1], S. HRVATIN[1], C. WEINREB[2], A. KLEIN[2], C. C. HARWELL[1];
[1]Neurobio., [2]Systems Biol., Harvard Med. Sch., Boston, MA

Abstract: The septum is ventral forebrain structure responsible for the regulation of emotional states including anxiety, fear and depression. The septum contains an extremely diverse array of short- and long-range projecting GABAergic neurons distributed across its two histological subdivisions, the medial and lateral septal nuclei. Both of these regions are heavily interconnected with other brain areas through efferent and afferent projections. It is currently unclear how septal neuronal diversity and the wiring of its circuits are specified during development. We used a combination of single-cell RNA-seq, histology and genetics to study the

developmental trajectories by which embryonic septal progenitors give rise to different types of neurons, and how these transition through subsequent maturation steps towards their mature function. We studied the septa of mice at six different developmental stages, finding key molecular differences between diverse types of neurons in the mature lateral and medial septum and the progenitor types that give rise to them. We present evidence in support of a general model for the specification of diverse septal neuron subtypes. Our results provide novel insights into the assembly of the complex circuitry underlying the regulation of internal states carried out by the septum.

Disclosures: M. Turrero Garcia: None. **S. Hrvatin:** None. **C. Weinreb:** None. **A. Klein:** None. **C.C. Harwell:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Title: Identification of Emx2 targets in early corticogenesis utilizing a proteomics approach

Authors: *A. MOHAMMED[1], H. MORIN[1], A. SANYANG[1], J. VELAZQUEZ[1], M. TIGGES[2], A. M. STOCKER[1];
[1]Biosci., [2]Chem. and Biochem., Minnesota State Univ. Moorhead, Moorhead, MN

Abstract: Transcription factors (TFs) are proteins that positively or negatively regulate gene expression. This regulatory control enables genes to be expressed in the correct cells at the appropriate amount in each cell of an organism. Homeodomain TFs have been shown to play important roles in imparting cellular and regional identity during embryonic development. Emx2 is a homeodomain TF that participates in the regulation of a number of important developmental processes including area fate decisions (i.e. area patterning); migration and lamination; cortical specification; and the switch from neuronal to glial production in neural progenitors. Previous studies have investigated changes in transcription following Emx2 deletion, however many were done at late embryonic time points after Emx2 has been downregulated and thus after many of the developmental events detailed. Furthermore, transcriptomic based studies are unable to provide information on the abundance or diversity of protein products. To circumvent these issues we utilized label-free proteomic analysis by ultra high performance liquid chromatography coupled with tandem mass spectrometry (UPLC-MS/MS) to identify changes in protein expression between different embryonic brains of Emx2 mutant mice. Brains were harvested at embryonic day 13.5, when neurogenesis in the telencephalon and Emx2 expression are both abundant. A nestin promoter driven overexpression and a cortex specific deletion mediated by

Emx1 driven Cre-recombinase of Emx2 were compared to control tissues with intact endogenous Emx2 expression. Differences in protein expression and abundance will be explored.

Disclosures: A. Mohammed: None. **H. Morin:** None. **A. Sanyang:** None. **J. Velazquez:** None. **M. Tigges:** None. **A.M. Stocker:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: Canadian Institutes for Health Research
Foundation for Fighting Blindness (Canada)

Title: Temporal transcription factors interact with chromatin remodelling complexes to regulate competence transitions during neural development

Authors: S. SHAH[1], C. JOLICOEUR[2], T. DANG[1], ***P. MATTAR**[1], *M. CAYOUETTE[2]; [1]Regenerative Med., OHRI, Ottawa, ON, Canada; [2]Cell. Neurobio., IRCM, Montreal, QC, Canada

Abstract: During development, neural progenitor cells dynamically alter their potential in order to generate different types of neurons and glia in the correct sequences. A number of 'temporal transcription factors' have been identified that are dedicated to controlling transitions in progenitor multipotency, but the molecular mechanism employed by this class of transcription factors remains unclear. To identify the molecular pathway used by temporal factors to regulate competence states in neurogenesis, we focused on the zinc finger transcription factor *Casz1* - the mammalian orthologue of *Drosophila castor*. We have previously shown that Casz1 encodes late multipotency in murine retinal progenitor cells. Here, focusing on postnatal retinal development, we show that *Casz1* controls the rod versus Müller glia cell fate choice. Next, we performed Bio-ID proteomics, which revealed that Casz1 interacts with the Mi2/Nurd complex in postnatal retinal progenitors. Finally, we show that both the Mi2/Nurd complex and the downstream polycomb repressor complex are required for Casz1 to promote the rod fate and suppress gliogenesis. Since other temporal transcription factors have been shown to interact with these complexes in other contexts, we propose that temporal transcription factors modulate the functions of the same co-factor complexes in a step-wise fashion in order to regulate competence transitions.

Disclosures: S. Shah: None. **C. Jolicoeur:** None. **P. Mattar:** None. **M. Cayouette:** None. **T. Dang:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Title: The role of E-proteins Tcf3 and Tcf12 in ventral telencephalon development

Authors: *M. J. TALLEY[1,2], D. NARDINI[1], L. EHRMAN[1], R. R. WACLAW[1];
[1]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH; [2]Univ. of Cincinnati, Cincinnati, OH

Abstract: The mouse telencephalon contains progenitor cells that eventually differentiate into numerous subtypes of neurons, myelinating oligodendrocytes, and astrocytes. In most cases, these diverse cells are generated from progenitor cells that are spatially and temporally distinct at specific stages of development. Proper progenitor proliferation and differentiation are required to establish regional identify and to specify the correct balance of cell types in the brain. The class I basic helix-loop-helix (bHLH) transcription factors, also called E-proteins, were thought to be ubiquitously expressed and play key roles in brain progenitor dynamics largely through their interactions with pro-neural and pro-glial class II bHLH transcription factors. However, specific roles of E-proteins have been elusive as their expression has not been fully characterized in the developing forebrain and germline single E-protein KOs have not identified specific roles during forebrain progenitor cell development or differentiation. Using *in situ* hybridization and immunofluorescence, we have characterized Tcf3, Tcf4, and Tcf12 expression in the developing telencephalon. To address a role for Tcf3 and Tcf12 during development, we generated conditional knockouts using *Olig2*$^{cre/+}$ to target the ventricular zone progenitor cells in the ventral telencephalon and the entire oligodendrocyte lineage. We did not detect a phenotype in *Tcf3* or *Tcf12* single conditional mutants. However, our preliminary data has revealed that combined loss of *Tcf3* and *Tcf12* results in developmental defects in early forebrain progenitor cells, oligodendrocyte progenitor cell generation, and oligodendrocyte differentiation. Our future directions will focus on the mechanism by which Tcf3 and Tcf12 impact ventral telencephalon progenitors and oligodendrogenesis.

Disclosures: M.J. Talley: None. **D. Nardini:** None. **L. Ehrman:** None. **R.R. Waclaw:** None.

Poster

457. Mechanisms of Cell Fate

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Program #/Poster #: 457.20/A20

Topic: A.01. Neurogenesis and Gliogenesis

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NIH Grant K08EY027093
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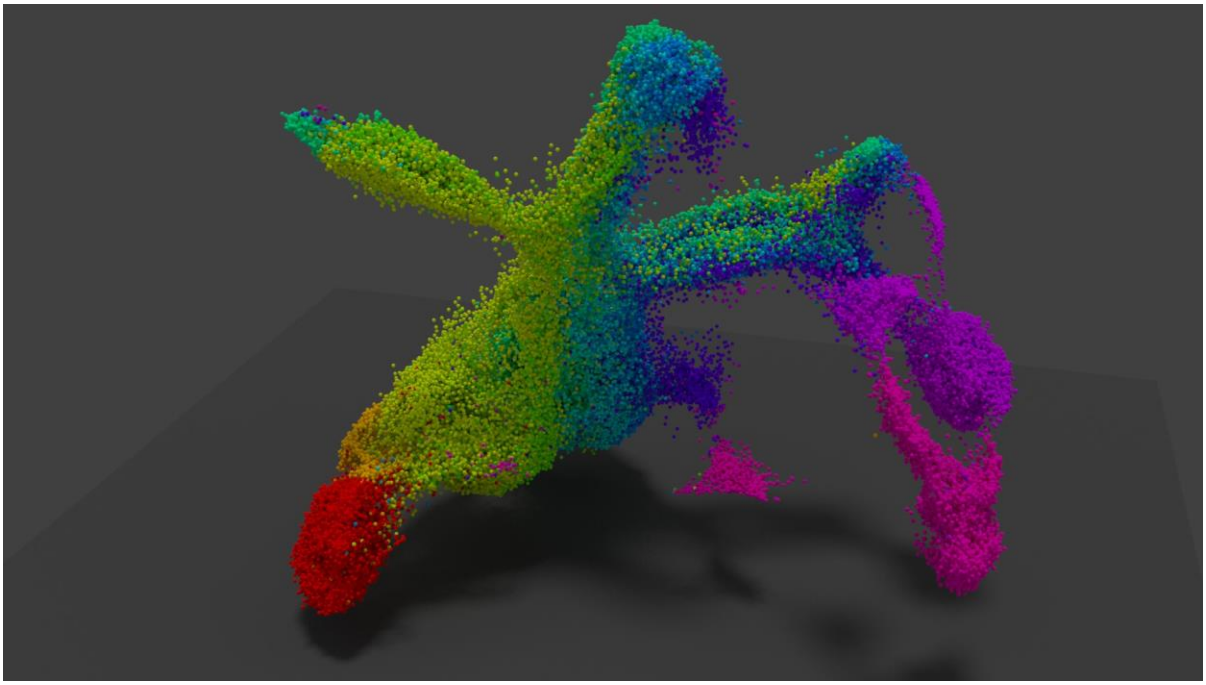
Title: Comprehensive single-cell RNA-seq analysis of murine retinal development identifies NFI factors as regulators of mitotic exit and late-born cell specification

Authors: B. S. CLARK*[1], G. STEIN-O'BRIEN*[2], F. SHIAU[7], G. H. CANNON[1], E. DAVIS-MARCISAK[3], T. SHERMAN[4], C. SANTIAGO[5], T. V. HOANG[5], F. RAJAII[5], R. E. JAMES-ESPOSITO[6], R. GRONOSTAJSKI[8], E. J. FERTIG[4], ***L. A. GOFF**[1], S. BLACKSHAW[9]; [1]Neurosci., [2]Neurosci. & Oncology, [3]Human Genet., [4]Oncology, [6]Solomon H. Snyder Dept. of Neurosci., [5]Johns Hopkins Univ. Sch. of Med., Baltimore, MD; [7]Ophthalmology and Visual Sci., Washington Univ., St. Louis, MO; [8]Univ. at Buffalo, Buffalo, NY; [9]Johns Hopkins Univ, Sch. Med., Baltimore, MD

Abstract: Precise temporal control of gene expression in neuronal progenitors is necessary for correct regulation of neurogenesis and cell fate specification. However, the cellular heterogeneity of the developing CNS has posed a major obstacle to identifying the gene regulatory networks that control these processes. To address this, we used single-cell RNA sequencing to profile ten developmental stages encompassing the full course of retinal neurogenesis. This allowed us to comprehensively characterize changes in gene expression that occur during initiation of neurogenesis, changes in developmental competence, and specification and differentiation of each major retinal cell type. We identify NFI transcription factors (Nfia, Nfib, and Nfix) as selectively expressed in late RPCs and show that they control bipolar interneuron and Müller glia cell fate specification and promote proliferative quiescence. To futher explore this developmental system, we developed a novel computational workflow which defines latent spaces from a source scRNA-seq dataset and evaluates these latent spaces in independent target datasets via transfer learning. Application to the developing mouse retina reveals intrinsic relationships across biological contexts and assays, while avoiding batch effects and other technical features associated with current single cell measurement techniques. We compare the dimensions learned

in this source dataset to adult mouse retina, a time-course of human retinal development, select scRNA-Seq datasets from developing brain, ATAC-Seq data, and a murine cell type atlas to identify shared biological features. These data and tools provide a comprehensive picture of the transcriptional landscape of the developing retina, and are used to identify shared and unique transcriptional signatures of cellular features across diverse developmental systems in the CNS and beyond.



Disclosures: **B.S. Clark*:** None. **G. Stein-O'Brien*:** None. **F. Shiau:** None. **G.H. Cannon:** None. **E. Davis-Marcisak:** None. **T. Sherman:** None. **C. Santiago:** None. **T.V. Hoang:** None. **F. Rajaii:** None. **R.E. James-Esposito:** None. **R. Gronostajski:** None. **E.J. Fertig:** None. **L.A. Goff:** None. **S. Blackshaw:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.21/A21

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grant-in-Aid for Scientific Research (C) JP18K06067

Title: DNA methylome identify differentiation potential of NS/PCs during brain development

Authors: *T. SANOSAKA[1], T. IMAMURA[2], K. NAKASHIMA[2];
[1]Kieo Univ. Sch. of Med., Tokyo, Japan; [2]Kyushu Univ., Fukuoka, Japan

Abstract: Epigenetic regulation during *in vivo* specification of CNS stem cells are still poorly understood. Here we report comparative methylome analyses of directly sampled cortical neural stem and progenitor cells (NS/PCs) at different development stages, as well as those of terminally differentiated cortical neurons, astrocytes and oligodendrocytes. We found that sequential specification of cortical NS/PCs is regulated by two successive waves of demethylation at early and late development stages, respectively, which are responsible for the establishment of neuron- and glia-specific low methylated regions (LMRs). We further found that Nuclear factor I (NFI) induces demethylation of glial lineage-specific genes, orchestrating the onset of glial differentiation. We provide evidence showing that eventually DNA methylation of neuronal-specific LMRs is required to maintain glial specific-epigenotypes, essentially by silencing neuronal genes. Our data highlight the *in vivo* implications of DNA methylation dynamics in shaping epigenomic features that confers lineage competence in the developing CNS.

Disclosures: T. Sanosaka: None. **T. Imamura:** None. **K. Nakashima:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.22/A22

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS097525
NIH Grant MH112328

Title: Molecularly dissociable roles of chromatin remodeling in cortical development

Authors: J. M. KEIL, A. QALIEH, M. M. LAM, L. SHI, *K. Y. KWAN;
Univ. of Michigan, Ann Arbor, MI

Abstract: Emerging human genetic findings have convergently implicated dysregulation of chromatin as a key contributor to disorders of brain development. Recent studies have shown that altered chromatin function can perturb neural cell fates, cell-type dependent gene expression, or neuronal plasticity via defective transcriptional regulation. However, in addition to gene transcription, chromatin also plays key roles in other processes on DNA, including DNA damage detection and repair. Here, we found that disruption of chromatin remodeling in cortical neural progenitor cells impairs DNA double-strand break repair, thus triggering p53 activation, robust apoptosis, and microcephaly. Transcriptome analysis revealed that this function of chromatin

remodeling is molecularly distinct from direct regulation of transcription. Furthermore, chromatin-mediated DNA repair showed developmental stage and cell-type dependence. Thus, chromatin remodeling is required for the maintenance of genome stability during cortical development, and its disruption can contribute to neurodevelopmental disorders in a transcription-independent manner.

Disclosures: J.M. Keil: None. **A. Qalieh:** None. **M.M. Lam:** None. **L. Shi:** None. **K.Y. Kwan:** None.

Poster

457. Mechanisms of Cell Fate

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 457.23/A23

Topic: A.01. Neurogenesis and Gliogenesis

Title: Chromatin remodeling and non-cell-autonomous regulation of cortical connectivity

Authors: *D. J. DOYLE, A. QALIEH, M. M. S. LAM, K. Y. KWAN;
Mol. and Behavioral Neurosci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Chromatin remodeling dynamically regulates spatiotemporal gene expression and cell-type specific identity. In cortical development, chromatin regulation can function cell-autonomously to specify or refine the molecular identity of diverse neuronal subtypes during neurogenesis. During the subsequent assembly of neural circuitry, chromatin regulation can also mediate non-cell-autonomous mechanisms, potentially by directing spatiotemporal expression of axon guidance molecules and their cell surface receptors. With the potential to mediate lasting molecular changes, chromatin remodelers are well-positioned to regulate multiple aspects of cortical development. However, potential cell-type dependent roles of chromatin remodelers in cortical neuron identity and connectivity have remained largely unexplored. Here, we found that the mammalian SWI/SNF remodeling complex plays a key role in the maintenance of cell type-specific neuronal transcriptomes. In the absence of this transcriptional regulation, cortical connectivity was widely disrupted as a combined result of both cell-autonomous and non-cell-autonomous dysregulation. Therefore, the mammalian SWI/SNF chromatin remodeling complex plays cell- and non-cell-autonomous roles in the specification of neuronal identity and wiring of cortical connectivity.

Disclosures: D.J. Doyle: None. **A. Qalieh:** None. **M.M.S. Lam:** None. **K.Y. Kwan:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.01/A24

Topic: A.07. Developmental Disorders

Support: NIH R01MH110630
NIH R00MH094409
NICHD T32HD007475

Title: Successful prediction of scan task and individual identity, but not ASD status, from functional connectomes in an extensively and densely sampled multiband fMRI dataset

Authors: *L. BYRGE, D. P. KENNEDY;
Indiana Univ., Bloomington, IN

Abstract: There is currently much interest in using functional connectivity (FC) MRI to identify neural biomarkers of ASD, despite many inconsistent and null results in the literature. Such failures to replicate could potentially stem in part from limitations in scan resolution and scan duration as well as the use of resting state protocols that lack a shared stimulus. Here, we evaluate FC similarity and diagnosis prediction in a sample of adults with ASD and controls using extensively and densely sampled fMRI data from each subject. We acquired multiband resting-state and video-watching scans (813ms TR) from 29 adult controls and 22 matched individuals with ASD across two scan sessions, comprising about 2 hours of functional data per individual. Preprocessing and FC matrix construction are described in Byrge & Kennedy (2018); we examined two parcellations and several approaches to addressing data quality (multiple censoring thresholds with and without downsampling to equate data quantity). We found that within-individual similarity of functional connectomes did not differ across groups after controlling for data quality covariates, indicating equivalent reliability across scans. Individual connectomes were highly distinct from other individuals, such that we could predict subject identity with ~98% accuracy. Using the same fingerprinting method, however, we could not predict subject diagnosis (under 62% accuracy). In contrast, this same method could be used to predict scan type (rest/video) with ~97% accuracy, indicating that scan type elicited a stronger common FC pattern than diagnosis. Similar results were obtained using classifiers trained on only the most informative FC edges and controlling for data quality (~60% accuracy for diagnosis; ~97% accuracy for scan type). Consistent with the diagnosis prediction results, group differences in FC similarity to controls were small and sensitive to choices of parcellation and data quality approach. We found no evidence for a shared ASD-specific pattern of FC; in no case was FC similarity to ASD individuals higher in the ASD group. Enhancing scan resolution, increasing scan duration, and adding video scans were thus not sufficient to reveal an FC-based

biomarker of ASD, despite high-quality data that permitted near-perfect prediction of individuals and scan task. Our results suggest that the development of useful biomarkers and mechanistic insight into neural differences in ASD may require employing and developing analytic techniques that operate fundamentally at the individual or subgroup level, rather than at the group level where no robust systematic differences were observed.

Disclosures: L. Byrge: None. **D.P. Kennedy:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.02/A25

Topic: A.07. Developmental Disorders

Support: Neurobiology of Language Dysfunction of Autism Spectrum Disorders 7R01HD051747 NICHD

Title: Amygdala volume and social impairment in youth with autism spectrum disorders

Authors: *Y. KIM, M. C. DUGGINS, J. DAVIS, K. PAULSON, C. DEMOPOULOS, B. KOPALD, K. DEPLONTY, J. D. LEWINE;
The Mind Res. Network, Albuquerque, NM

Abstract: Social impairment is a defining characteristic of Autism Spectrum Disorder (ASD). Identification of correlated biomarkers has the potential to improve early diagnosis, elucidate neurobiological mechanisms, and provide novel metrics for tracking the effectiveness of treatment. Although there does not appear to be a single convergent neurobiological etiology for all ASDs, there is mounting evidence for distinct patterns of structural and functional compromise in ASD sub-types. Previous research has highlighted the role of the amygdala in social impairment. The present study aims to expand and confirm previous research investigating (1) amygdala structural differences between subjects with an ASD and controls and (2) the relevance of the amygdala to social impairment phenotype in ASD. An automated, MRI region-of-interest pipeline based on FreeSurfer, was used to measure total intracranial volume and right and left amygdala volumes in 22 children and adolescents with an ASD (16 males, 6 females) and 12 typically developing controls (8 males, 4 females). Both absolute and relative amygdala volume (corrected for total intracranial volume) were examined as correlates of social impairment. Participants were assessed using the Social Responsiveness Scale (SRS) as a measure of the clinical phenotype of social impairment. There was no group difference in absolute or relative amygdala volumes and intracranial volume. However, strong correlations between amygdala volumes and SRS scores were found in ASD group. Regression analysis revealed increased amygdala volumes (both right and left hemispheres) were significantly

correlated with higher SRS scores in participants with ASD. That is, greater amygdala volume was associated with greater social impairment in the ASD group. Such a correlation was not seen in the control group. Most previous research on amygdala structure in the ASDs has focused on young children with ASD. There, it has been shown that young children with autism have greater amygdala volumes than age matched control subjects. As has been reported by some other, and is seen in our data, this difference does not appear to be maintained as children get older. The data thereby suggest altered developmental pathways in autism. The data also indicate that the relationship between amygdala volume and social impairment is complex and only seen in the autism group. Nevertheless, amygdala volume may prove to be a useful biomarker of social impairment in the ASDs. Future longitudinal studies will help to clarify relevant developmental trajectories. These findings have implications for future identification and intervention to support individuals with ASD.

Disclosures: **Y. Kim:** None. **M.C. Duggins:** None. **J. Davis:** None. **K. Paulson:** None. **C. Demopoulos:** None. **B. Kopald:** None. **K. DePlonty:** None. **J.D. Lewine:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.03/A26

Topic: A.07. Developmental Disorders

Title: Microbiota transplant intervention shows promising results in some children with autism spectrum disorder (ASD)

Authors: *H. B. WALKER[1], T. MIDTVEDT[2];
[1]Biomed Clin., Oslo, Norway; [2]Dept. of Microbiology, Tumor and Cell Biol., Karolinska Institutet, Stockholm, Sweden

Abstract: For most biochemical pathways there are different “security pathways”, which in an exposed first generation may impose a shut-down or activation of genes with other consequences than in second generation. Current scientific data suggests that many illnesses may stem from the similar, underlying patho-physiological process as autism. The second generations’ exposure will likely lead to compounded epigenetic factors. We are born germfree. Microbiota will develop in specific order-in a window of establishment - during the first two years of life. If a window is missed, it may give lifelong consequences. Since the 1950’s infants have been exposed to more xenobiotics before the age of 2 than ever before (new xenobiotics -vaccines, additives, pharmaceuticals, antibiotics, etc.). All of these influences upon the establishment of a healthy microbiota. Most often children with autism have a different - dysbiotic - microbiota then controls. The number of children diagnosed with ASD have been rising in the past decades. It may indicate that people with a certain genetic DNA profile are more vulnerable to changes in

microbiota, which may affect their biochemical functions manifesting itself as autism. We have followed some families that have successfully regulated relevant functions in their ASD children with microbiota transplantation. Their successful regulation has been sustained as long as the children are receiving microbiota transplants. The children have regressed to an autistic behaviour after stopping receiving transplant. It seems that a systematic transplantation is necessary for regulation of dysbiosis- at least for a longer period. Cases will be presented.

Disclosures: H.B. Walker: None. **T. Midtvedt:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.04/A27

Topic: A.07. Developmental Disorders

Support: Neurochlore

Title: Term or preterm cesarean section delivery transiently alters but does not lead to long-term detrimental consequences in mice

Authors: M. CHIESA[1,2], B. RIFFAULT[1,2], H. RABIEI[1,2], ***D. C. FERRARI**[1,2], Y. BEN-ARI[1,2]; [1]Neurochlore, Marseille, France; [2]Ben-Ari Inst. of Neuroarcheology (IBEN), Marseille, France

Abstract: Delivery is one of the most complex biological processes in mammals which involves hormonal and mechanical stimuli that together allow the survival and development of the newborn. Alterations to the time and mode of delivery could lead to modification of survival functions and have been hypothesized to promote the emergence of neurodevelopmental disorders. Epidemiological studies have controversially suggested that cesarean section (C-Section) delivery might increase the risk of neurodevelopmental disorders including Autism Spectrum Disorders (ASD). Yet, the complexity and heterogeneity of factors associated with delivery render existing epidemiological studies debatable. We have recently shown in an experimentally controlled mouse model of C-section delivery that mice born by term or preterm C-section did not present long-term autistic-like behavioral or physiological deficits. Nevertheless, mice born by preterm C-section presented early transient neuronal and communicative defects. Our recent results with the iDISCO clearing method reveal global modifications in the brains of preterm C-section delivered mice, and the alterations in communicative behaviors are due to the association between C-section delivery and preterm birth, and not to either deviation to birth on its own. Our results suggest that preterm C-section delivery might impact early brain development, rendering it more vulnerable to perinatal and postnatal insults. Our work sheds light on the intricacy of birth alterations and might explain the disparities reported in epidemiological studies.

Disclosures: **M. Chiesa:** A. Employment/Salary (full or part-time):; Neurochlore. **B. Riffault:** A. Employment/Salary (full or part-time):; Neurochlore. **H. Rabiei:** A. Employment/Salary (full or part-time):; Neurochlore. **D.C. Ferrari:** A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore. **Y. Ben-Ari:** A. Employment/Salary (full or part-time):; Neurochlore. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurochlore.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.05/A28

Topic: A.07. Developmental Disorders

Support: NIMH grant R01 MH112734-01

Title: Sensorimotor issues and core clinical symptoms in autism spectrum disorder (ASD)

Authors: S. BRIDWELL[1], G. GABRIELLI[2], *J. BARTOLOTTI[1], M. W. MOSCONI[1]; [1]Life Span Inst., Univ. of Kansas, Lawrence, KS; [2]Weinberg Col. of Arts and Sci., Northwestern Univ., Evanston, IL

Abstract: Background: Sensorimotor issues are common in autism spectrum disorder (ASD), and they are associated with worse functional outcomes in patients. It is possible that atypical sensorimotor development interferes with the maturation of core social-communication and cognitive systems in ASD. Characterizing sensorimotor impairments and their relationship to social-communication and cognitive symptoms of ASD thus holds promise for identifying key mechanisms of core symptom traits.
Methods: Sixty-six individuals with ASD (57 male, 9 female) and 83 age-, sex- and IQ-matched typically developing (TD) controls (50 male, 33 female) performed a test of manual motor control. During this test, participants viewed a horizontal white force bar that moved upward with increased force and a horizontal red stationary target bar that turned green at the beginning of each trial. Participants were instructed to press on two precision load cells with their thumb and index finger and maintain the force bar at the level of the target bar for 8- or 15- seconds. The target force level was varied at 15%, 45%, and 85% of the participants maximum voluntary contraction (MVC). The variability (SD) and regularity (or approximate entropy, ApEn) of participants' sustained force were examined. Manual motor behavior was examined in relation to clinical ratings of ASD severity, including the social communication questionnaire (SCQ), the social reciprocity scale (SRS-2), and the repetitive behavior scale – revised (RBS-R)
Results: For force SD, a group x sex interaction was observed (F_1=4.9, p=.03); males with ASD

showed elevated force SD compared to male TD controls (p=.07), but females with ASD and TD females did not show any differences in force SD (p=.15). Greater force SD was associated with more severe RBS-R rated repetitive behaviors (r=.32, p<.001) and SRS-2 ratings of ASD symptoms (r=.31. p=.05). Lower ApEn was associated with more severe RBS-R rated repetitive behaviors in ASD (r=-.31, p<.001) and more severe ASD symptoms on the SCQ (r=-.52, p<.001) and SRS (r=-.33, p=.03).
Conclusions: We examined a large cohort of individuals with ASD and document new evidence that patients show a reduced ability to precisely and dynamically adjust motor output in response to sensory feedback. Importantly, increased force variability and regularity each were associated with more severe ASD symptoms suggesting atypical sensorimotor processing may interfere with the development of social-communication and behavioral flexibility abilities in ASD, or that these separate sets of issues reflect common pathophysiological or developmental processes.

Disclosures: S. Bridwell: None. **G. Gabrielli:** None. **J. Bartolotti:** None. **M.W. Mosconi:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.06/A29

Topic: A.07. Developmental Disorders

Support: HRSA Grant R40MC19926

Title: Gastrointestinal symptomatology is associated with amygdalar reactivity to negative facial affect in autism spectrum disorder

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Abstract: Autism spectrum disorder (ASD) is characterized by repetitive behaviors and impaired social communication, but gastrointestinal (GI) symptoms are often reported as well. Alterations in endocrine and psychophysiological measures of stress reactivity have been shown to be associated with increased GI symptomatology in ASD. Furthermore, presence of a co-occurring anxiety disorder significantly enhances the relationship between GI symptoms and the psychophysiological response to stress. Existing studies have also shown that atypical emotional-face processing in ASD is associated with altered brain activity, measured by functional magnetic resonance imaging (fMRI), compared to controls. It is not known if reactivity in brain

areas that respond to fear and anxiety is associated with GI symptoms in ASD. Therefore, to begin understanding neural correlates of altered stress reactivity associated with GI symptoms in ASD, this study assessed the potential relationship between GI symptomatology and amygdalar reactivity during presentation of emotional faces in individuals with ASD. In an initial pilot investigation, fMRI data from 12 high-functioning adults with ASD was processed using FMRIB Software Library (FSL) version 6.0.0. to determine differences in amygdalar blood oxygen level dependent activation during presentation of fearful and angry faces during face-matching tasks presented in the scanning session. GI symptomatology was assessed using scores created from the Autism Treatment Network GI Symptoms Inventory, such that higher scores indicate increased frequency, duration, and severity of GI symptoms over the past month. Relationships between amygdalar reactivity and GI symptomatology scores were assessed using R to perform one-sample *t*-tests. Initial results from this pilot investigation revealed a significant positive correlation between changes in activation of bilateral amygdala when looking at faces with fearful and angry expressions compared to neutral expressions and changes in GI symptomatology. In addition, a significant positive correlation was found between changes in activation of the right amygdala when viewing faces with an angry expression compared to no stimulus and GI symptomatology. As such, these results suggest that some individuals with ASD may experience an augmented anxiety response to negative facial affect which is associated with increased GI symptomatology. More work is needed to determine whether a causal relationship between these common aspects of ASD exists. Obtaining this information may help with the development of new treatments for those with ASD and GI problems to increase their quality of life.

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Poster

458. Autism: Physiology, Systems, and Behavior

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Topic: A.07. Developmental Disorders

Support: NIH R21-MH114095

Title: Associations between resting-state EEG alpha-band power and atypical sensory processing and social communication impairments in children with autism spectrum disorder

Authors: *S. PIERCE, G. KADLASKAR, B. KEEHN;
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Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder diagnosed on the basis of impairments in social communication and the presence of restricted and repetitive behaviors, including atypical responsivity to sensory input. Neural oscillations, as measured by electroencephalogram (EEG), play a key role in brain function and are associated with a variety of perceptual and cognitive processes. In particular, resting alpha (8-12 Hz) levels are associated with peripheral measures of autonomic activity. Previous studies have attempted to identify the mechanism(s) associated with sensory processing abnormalities in ASD with contradictory results. Thus, the objective of this study is to examine the differences in alpha-band power in children with ASD and their typically developing (TD) peers, and to investigate the association between alpha power and measures of ASD symptomatology. Participants included 21 children with ASD and 17 age- and sex-matched TD children. EEG data were recorded for 3, 2-minute blocks of eye-open resting state. Participants saw a black central crosshair was presented on a grey background, and were instructed to relax, remain still, and to look at the crosshair. EEG was recorded using 128-channel Geodesic electrode array. Alpha power was extracted from frontal, central, and posterior regions of interest (ROIs). The Sensory Profile - 2 (SP-2) and the Autism Diagnostic Observation Schedule (ADOS) were used as measures of sensory processing differences and sociocommunicative impairment. Findings from EEG analyses revealed that absolute alpha levels were significantly reduced in the ASD group compared to the TD group, particularly in the posterior ROI (Figure 1). For the ASD group, no relationship was found between the SP-2 subscales and the alpha levels. However, there was significant association between alpha power and ASD severity scores as measured using the ADOS. These findings suggest that children with ASD may be more physiologically aroused compared to their TD peers, and that this may be associated with greater ASD symptomatology.

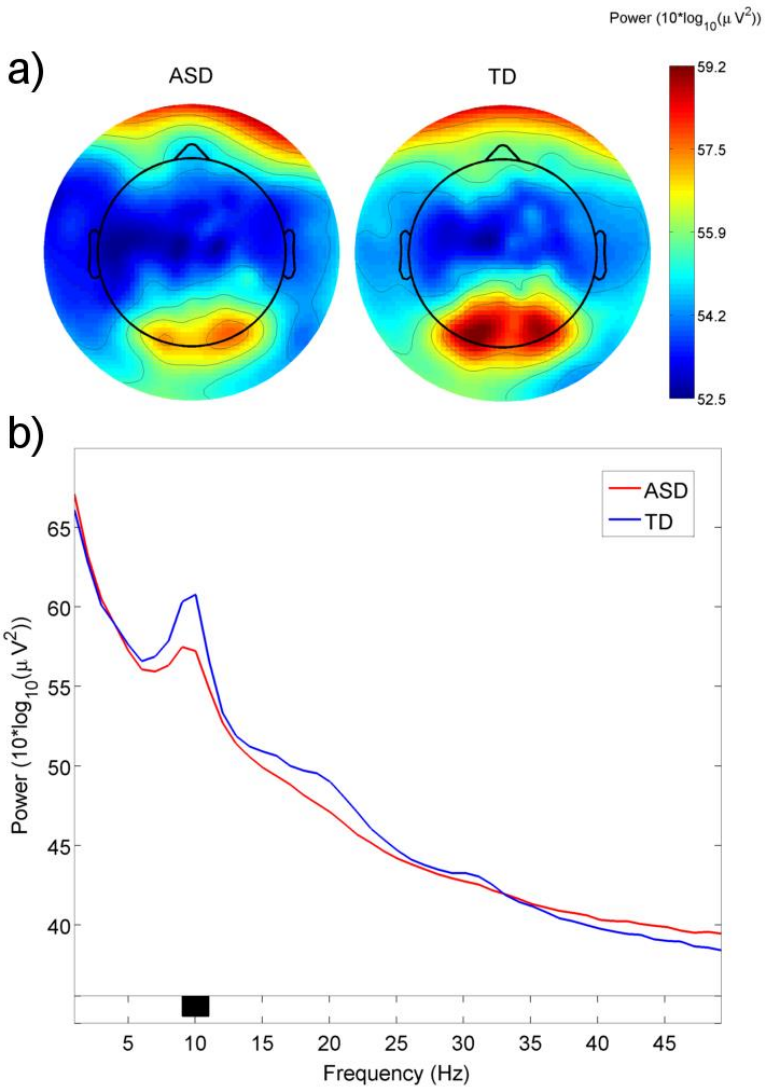

Figure 1: (a) Scalp maps of resting-state alpha (8–12 Hz) power for the autism spectrum disorder (ASD; left) and typically developing (TD; right) groups. (b) Spectra for each group from the posterior region of interest (ROI). Only significant differences in power show by blank bar on x-axis within alpha-band.

Disclosures: S. Pierce: None. **G. Kadlaskar:** None. **B. Keehn:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

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Topic: A.07. Developmental Disorders

Support: NIH Grant MH092696
NIH Grant MH112734
NIH Grant U54HD090216

Title: Differential utilization of visual and proprioceptive information for postural control stability in individuals with autism spectrum disorder (ASD)

Authors: *Z. WANG[1], J. CHEN[1], E. IN[1], W. MCKINNEY[2], Z. LI[1], M. MOSCONI[2];
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Abstract: Sensorimotor impairments are common in autism spectrum disorder (ASD), although the extent to which sensory processing issues affect motor control and movement coordination in individuals with ASD is not well understood. Previous studies have suggested that individuals with ASD show increased postural sway variability in stances during which either visual or proprioceptive information is occluded. No known study to date has examined the interactive effect of visual and proprioceptive inputs on postural stability in individuals with ASD. The aim of this ongoing research is to fill this critical knowledge gap by quantifying individuals' postural sway variability during tasks with and without the availability of visual and proprioceptive information. Twenty-eight school-aged children with ASD and 11 age-, sex- and IQ- matched healthy controls participated in tests of static stance on an AMTI force platform. During the assessment, a pair of lightweight tendon vibrators (TVs) was attached on participants' Achilles tendon of the ankle joints. When turned on, both TVs vibrate at a high frequency of 80Hz to create a transient proprioceptive illusion of lengthened Achilles tendon of both legs. Participants completed tests with and without the TVs (i.e., TV_{on} vs. TV_{off}) and lights on and off (LT_{on} vs. LT_{off}). Postural sway variability was assessed using the center of pressure (COP) trajectory length and COP standard deviation in the anterior-posterior (COP_{AP}) and mediolateral (COP_{ML}) directions. Both individuals with ASD and healthy controls showed increased COP trajectory length and COP_{AP} standard deviation during TV_{on} conditions regardless of the light condition. The COP trajectory length of patients, relative to controls, showed a larger increase during TV_{on} compared to TV_{off} conditions. Individuals with ASD showed increased COP_{AP} and COP_{ML} standard deviation compared to controls across all task conditions. Proprioceptive information serves as the primary sensory source for gross motor activities including postural control. Our results suggest that postural instability in individuals with ASD and healthy controls is more severely impacted by proprioceptive illusions compared to perturbations in visual feedback.

Although both individuals with ASD and TD controls were affected by the proprioceptive illusion, postural stability was more strongly impacted in ASD suggesting a heightened dependency on proprioceptive information during standing. These findings inform a more mechanistic view of postural issues in ASD indicating that over-reliance on proprioceptive feedback may interfere with stability in patients.

Disclosures: Z. Wang: None. **J. Chen:** None. **E. In:** None. **W. McKinney:** None. **Z. Li:** None. **M. Mosconi:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.09/A32

Topic: A.07. Developmental Disorders

Support: Kaken 17H03563

Title: A possible involvement of ca^{2+}-dependent activator protein for secretion 2 (CAPS2) in regulating release of the hypothalamic neuropeptide oxytocin that hs pivotal role in social behavior

Authors: *S. FUJIMA[1], R. YAMAGA[1], H. MINAMI[1], R. MANIWA[1], N. AMEMIYA[1], M. ABE[2], K. SAKIMURA[3], Y. SHINODA[4], Y. SANO[1], T. FURUICHI[1];
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Abstract: CAPS family proteins (CAPS1 and CAPS2) promote exocytosis of dense-core vesicles containing neuropeptides, peptide hormones and monoamine neurotransmitters. We previously reported that CAPS2 knockout mice not only showed decreased release of neurotrophic factors and consequently impaired synaptic development and function but also displayed abnormalities in social and anxiety behavior. There are multiple reports that suggest a possible link between autism spectrum disorder (ASD) and CAPS2, due to the fact that alterations in CAPS2 gene and its expression (*de novo* copy number variation, single nucleotide variation, aberrantly-increased expression of a rare splicing variant) have been found in some ASD patients. However, it is yet unknown how failed CAPS2-mediated release mechanism contributes to ASD risk. We also showed that CAPS2 is expressed in the hypothalamic paraventricular nucleus (PVN), producing neurohypophysial hormones oxytocin (OXT) and vasopressin (AVP) both of which are known to modulate social behavior in several animal species. From this point of view, we got an idea that abnormality of CAPS2 affects release of OXT and/or AVP, thereby resulting in impaired social behavior.To address this question, we

analyzed cellular expression of CAPS1 and CAPS2 in OXT- or AVP-positive neurons in the PVN. As a result, CAPS2 protein was largely localized in OXT and AVP neurons in the anterior than posterior PVN. CAPS1 protein was also expressed in approximately half of OXT neurons. CAPS2 and CAPS1 protein was also concentrated in the posterior pituitary (PP), in which OXT and AVP are secreted from the axon terminals to blood vessels. Next, we compared serum OXT levels between control and CAPS2 KO mice by OXT ELISA. As a result, CAPS2 KO mice showed decreased serum OXT levels compared to those of control mice. We also analyzed OXT immunoreactivity in the PP of mice with conventional KO and OXT neuron-specific conditional knockout (cKO) of CAPS2. We found accumulated levels of OXT in the PP of both CAPS2 KO and cKO mice compared to their control mice. These results suggest that CAPS2 plays a role in OXT secretion. Our preliminary data also suggest that both CAPS2 and CAPS1 probably regulate the release of social hormones OXT and AVP. Taken together, we suggest that a deficit in CAPS2-mediated release mechanism may be associated with OXT-related social behavior.

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Poster

458. Autism: Physiology, Systems, and Behavior

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.10/A33

Topic: A.07. Developmental Disorders

Support: NIH R21-MH114095

Title: Measures of tonic and phasic activity of the locus coeruleus - norepinephrine system in children with autism spectrum disorder

Authors: *B. KEEHN[1], G. KADLASKAR[1], R. MCNALLY KEEHN[2];
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Abstract: The locus coeruleus-norepinephrine (LC-NE) system, which is known to play an important role in arousal regulation and selective attention, has been shown to function atypically in individuals with autism spectrum disorder (ASD). For example, indirect measures of LC-NE activity, such as pupil diameter and event-related potential (ERP) P3 component, differ in individuals with ASD. However, no study to date has examined both tonic (pupil) and phasic (P3) indices of LC-NE activity in a single cohort of individuals with ASD. The objective of the present study is to investigate tonic and phasic LC-NE activity in children with ASD. Participants included 18 children with ASD and 20 age- and non-verbal IQ-matched typically developing (TD) children. The study consisted of separate baseline eye-tracking and odd-ball

ERP tasks. For the baseline paradigm, a black central crosshair was presented on a grey background, and participants were instructed to relax, remain still, and to look at the crosshair. For the odd-ball paradigm, stimuli were isoluminant shapes (small circle = standard [76% of trials]; large circle = target [12%]; square = novel [12%]) displayed on a gray background. Participants were instructed to respond via a button press when a large circle was presented. Pupil diameter was monitored using an EyeLink 1000 Plus remote eye-tracking system and EEG was recorded using 128-channel high-density Geodesic electrode array. Findings from baseline task revealed that individuals with ASD showed significantly increased pupil size compared to their TD peers ($p < .05$). For the odd-ball paradigm, mean amplitude of P3 component (400-600ms) was maximal at posterior leads, but did not differ between TD and ASD groups ($p = .53$). However, groups did differ in frontal channels, with the ASD group exhibiting significantly reduced amplitude compared to their TD peers ($p < .05$). For the ASD group, larger pupil size was associated with reduced P3 amplitude. Consistent with prior reports, our preliminary results show that children with ASD exhibit increased tonic (pupil) and reduced phasic (P3) activation of the LC-NE system. The preliminary findings add to the growing body of evidence that suggest that LC-NE system may function atypically in individuals with ASD.

Disclosures: **B. Keehn:** None. **G. Kadlaskar:** None. **R. McNally Keehn:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.11/A34

Topic: A.07. Developmental Disorders

Support: Tobacco Cure Funds Pennsylvania Department of Health
NIH R01MH116176

Title: Quantitative brain wide map of the oxytocin receptor in postnatally developing mouse brains

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Abstract: Oxytocin is an endogenous neuropeptide that plays a critical role in the development and expression of social behavior. The primary postsynaptic mediator of oxytocin signaling is the oxytocin receptor (OTR). OTR expression undergoes dramatic developmental shifts with

peak expression during early postnatal critical periods. Previous evidence suggests strong links between oxytocin receptor dysfunction and the pathogenesis of neurodevelopmental disorders such as autism spectrum disorder. Despite its significance to human health, knowledge of quantitative brain-wide spatial and temporal OTR expression patterns remain limited particularly in the early postnatal brain. Therefore, we imaged whole brain OTR expression patterns at the cellular resolution via serial two-photon tomography on two different transgenic mouse lines (OTR-eGFP and $OTR^{venus/+}$). Using newly generated 3D postnatal brain templates for early postnatal timepoints, we quantified OTR expressing cell density at postnatal days (P) P7, P14, P21, P28, and P56. These quantifications revealed that the heterozygote $OTR^{venus/+}$, but not the OTR-eGFP line, faithfully reports OTR expression at the cellular level. We found that there is significant temporal and regional heterogeneity in OTR expression patterns across cortical and subcortical regions. We then used OTR-Cre:Ai14 cumulative labelling to identify expression downregulation and not cell death as the main mechanism driving developmental OTR patterns. Moreover, immunohistochemistry showed that majority of OTR-expressing neurons in the cortical layers except layer 6b are glutamatergic at P21. These results provide quantitative data that is essential to understanding the OTR development in the mouse brain.

Disclosures: K.T. Newmaster: None. **Z. Nolan:** None. **U. Chon:** None. **M. Tabbaa:** None. **S. Hidema:** None. **K. Nishimori:** None. **E.A. Hammock:** None. **Y. Kim:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

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Program #/Poster #: 458.12/A35

Topic: A.07. Developmental Disorders

Support: NIMH 1R15MH118627-01

Title: Reduced VTA Drd2 expression increases sociability in adult mice

Authors: A. KHASNAVIS, B. SULAMAN, *B. ZUPAN;
Vassar Col., Poughkeepsie, NY

Abstract: The mouse model of Fragile X Syndrome (FXS), the most common form of inherited intellectual disability and a leading known monogenic cause of autism caused by silencing of *FMR1*, exhibits hyperactivity, abnormal sociability, and sensory hyperreactivity. Our research suggests that a subset of the phenotype is programmed in part by maternal *Fmr1* genotype: haploinsufficiency of maternal *Fmr1* ($Fmr1^{+/-}$ or H) is sufficient to induce hyperactivity and hypersociability in genetically normal (WT; $Fmr1^{+/y}$) male offspring, indicating developmental sensitivity to maternal FMRP levels. Dopamine (DA) signaling modulates both activity and social behavior, the dysfunction of which is a core symptom of FXS and autism. Increased

activity of VTA DA neurons projecting to NAc increases while decreased activity decreases time spent with a novel same-sex conspecific. We've previously reported that both WT and KO offspring of FMRP deficient dams exhibit attenuated locomotor-reducing effects of dopamine autoreceptor 2 (D2aR) activation, suggesting that maternal FMRP deficiency may program altered sociability and hyperactivity by downregulating a negative feedback mechanism of DA signaling. Indeed, *Fmr1* H dam-derived male offspring show reduced VTA *Drd2* expression in VTA irrespective of their own *Fmr1* genotype. Here we asked if reduced VTA *Drd2* expression is sufficient to cause the hypersociability previously reported by our lab. We crossed C57Bl/6 *Drd2*$^{fl/fl}$ (B6.SJL-Slc6a3$^{tm1.1(cre)Bkmn}$/J) male with FVB *Fmr1* WT female mice to generate C57 x FVB F1 mice expressing *Drd2*$^{fl/+}$. *Fmr1* WT F1 offspring of H dams show hypersociability relative those reared by *Fmr1* WT dams, indicating that F1 hybrid mice are sensitive to maternal FMRP levels. Next, we co-injected TH-Cre (AAV9.rTH.PI.Cre.SV40, UPenn Vector Core) and DIO-EGFP (pAAV.synP.DIO.EGFP.WPRE.hGH, Addgene) viral vectors into the VTA of adult F1 *Drd2*$^{fl/+}$ mice, aiming to reduce *Drd2* expression by ~50% in TH+ cells. Preliminary qPCR data showed a 40% reduction in VTA *Drd2* expression by three weeks post-injection, so sociability and quinpirole sensitivity were assessed in a second cohort four weeks post-injection. Th-Cre+ mice exhibited increased sociability relative to GFP-injected controls, and failed to show quinpirole-induced reduction of locomotor activity. Following behavioral testing, *Drd2* expression in TH+ VTA neurons in these mice was confirmed by qPCR and those that failed to show reduced *Drd2* expression were excluded from analysis. Our data show that reduced VTA *Drd2* expression is sufficient to increase sociability in adult mice, phenocopying hypersociability of mice reared by *Fmr1* deficient dams.

Disclosures: **A. Khasnavis:** None. **B. Sulaman:** None. **B. Zupan:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.13/A36

Topic: A.07. Developmental Disorders

Support: NIH Grant K01MH103594
NIH Grant R21MH109775

Title: Mapping neural correlates to biological motion in school-aged children with autism using high density diffuse optical tomography

Authors: *A. M. SVOBODA[1], M. L. SCHROEDER[2], A. T. EGGEBRECHT[3];
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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by marked impairments in social communication and heightened restrictive and repetitive patterns of behavior. Understanding the disruption to neural systems underlying ASD will be crucial in early diagnosis and developing targeted treatments and interventions. However, traditional neuroimaging modalities like functional magnetic resonance imaging (fMRI) require participants to remain still in a loud, enclosed environment that can be challenging for children with ASD and limits imaging studies to primarily high-functioning children. To overcome these challenges while acquiring fMRI comparable images, we have developed high-density diffuse optical tomography (HD-DOT), a silent, wearable, and minimally constraining neuroimaging modality that can map brain function in a naturalistic environment more feasible for children with ASD. In the current study, we aim to validate the use of HD-DOT in children with ASD. We utilized a socially relevant stimulus paradigm consisting of scrambled and coherent point-like animations of biological motion. Biological motion is a well-validated paradigm that has been used in fMRI and eye-tracking studies to evaluate altered patterns of social perception and processing in those with ASD. It has indicated that compared to typically developing children, those with ASD show reduced contrasts to coherent vs scrambled motion in multiple cortical regions including the posterior temporal sulcus (pTS), parietal cortex, and dorsolateral prefrontal cortex (dlPFC). We collected HD-DOT data in 10 children with ASD age 8-13 years (5 females and 5 males) and 12 unaffected adults age 23-32 (8 females and 4 males) during the presentation of scrambled and coherent biological motion in a 24-second block design. Each block includes 12 seconds of scrambled followed by 12 seconds of coherent biological motion. Results indicate that, consistent with prior literature, participants demonstrate localized activity in dlPFC, pTS, and visual cortex, specifically in motion sensitive area MT. From these results, we conclude that HD-DOT is a suitable neuroimaging modality to detect responses from biological motion in children with ASD. Future directions include assessing differences in neural responses of TD children vs those with a diagnosis of ASD in their response to biological motion and using HD-DOT to measure brain activity in lower-functioning children including infants and toddlers at risk of ASD and school-aged children with more severe ASD.

Disclosures: **A.M. Svoboda:** None. **M.L. Schroeder:** None. **A.T. Eggebrecht:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

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Program #/Poster #: 458.14/A37

Topic: A.07. Developmental Disorders

Support: NIH Grant 2T32MH064913-16
NIH Grant
R01MH102272

Title: Sub-groups of sensory connectivity profiles in autism and typical development

Authors: *A. R. ZOLTOWSKI[1], M. D. FAILLA[2], C. OKITONDO[3], L. E. MASH[4], S. DAVIS[3], B. HEFLIN[5], B. ROGERS[1], C. J. CASCIO[2];
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Abstract: Sensory processing differences have been recently recognized as part of the diagnostic criteria for autism spectrum disorders (ASD), but these symptoms are highly heterogeneous across individuals. Individuals may differ both in the sensory system affected, and whether they show hyper- or hypo- responsiveness to these sensory stimuli. Efforts to identify subgroups of ASD with more similar within-group sensory responsiveness have typically focused on a phenotype-first approach, identifying groups by behavioral responses to sensory stimuli. We aimed to take a neurobiology-first approach and investigate subgroups of individuals based on brain networks, assessing connectivity between intrinsic networks and primary sensory regions. N=28 individuals with ASD (ages 8-54) and N=45 typically developing individuals (TD, ages 8-41) completed a resting-state fMRI scan. Subject-level networks were identified using independent component analysis and the components with the highest default mode and salience network overlap with templates from Yeo et al. (2011) were selected. Associations between these networks and visual, somatosensory, and interoceptive regions were calculated and used for k-means clustering to identify sub-groups of connectivity profiles. Relationships between the clusters and sensory signals (heart rate variability, HRV) and sensory awareness (body perception questionnaire, BPQ) were assessed. Two main clusters emerged across both our ASD and TD groups, primarily stratified by high versus low salience network connectivity with primary interoceptive cortex and secondary somatosensory cortex. The high connectivity cluster showed lower HRV than the low connectivity cluster (Cohen's d=0.38), indicating similar interoceptive signaling. However, ASD and TD individuals showed trends towards opposite patterns of self-reported body awareness by cluster (diagnosis by cluster interaction p-value=0.117). These results indicate trans-diagnostic subgroups based on salience network connectivity with somatic and interoceptive sensory regions. Further, these subgroups show consistently lower heart rate variability, suggesting that individuals with less variable interoceptive signals may attribute higher salience to these signals. However, the ASD and TD subgroups showed opposite patterns of reported body awareness. Future directions may include more intermediate variables (e.g., sensory integration measures) to fully understand the link between interoceptive connectivity patterns and behavioral sensory reports.

Disclosures: A.R. Zoltowski: None. **M.D. Failla:** None. **C. Okitondo:** None. **L.E. Mash:** None. **S. Davis:** None. **B. Heflin:** None. **B. Rogers:** None. **C.J. Cascio:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

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Program #/Poster #: 458.15/A38

Topic: A.07. Developmental Disorders

Support: Ontario Brain Institute

Title: Lateral and central nuclei volumes predict anxiety and depression scores in children with neurodevelopmental disorders

Authors: D. SEGUIN, **J. CHEN**, J. MARTINEZ-TRUJILLO, R. NICOLSON, *E. G. DUERDEN;
Western Univ., London, ON, Canada

Abstract: Previous research has indicated that alterations in the structural maturation of the basolateral and central nuclei of the amygdala are associated with anxiety behaviours in typically developing adults and children with autism spectrum disorder. This study investigated neurodevelopmental disorder diagnoses and basolateral and central amygdala nuclei volumes in relation to anxiety and depression scores in a large pediatric sample consisting of 233 individuals, aged 6-18 years. Parents completed the Child Behavior Checklist (CBCL) and the children underwent structural MRI at 3T (Tesla). The children received a research confirmed diagnosis of neurodevelopmental disorder. Children included in this study received a diagnosis of autism spectrum disorder (ASD, n=111), attention deficit hyperactivity disorder (ADHD, n=38), obsessive-compulsive disorder (OCD, n=27), or were typically-developing (n=57). Freesurfer software was used to automatically segment the amygdala into 9 subnuclei. A generalized linear model revealed that the left lateral and right central nuclei demonstrated significantly different volume sizes relative to typically developing controls ($p<0.05$), after controlling for total brain volume, age and gender. A subsequent analysis examined the interaction of disorder diagnosis and individual nuclei volume on anxiety and depression scores of the CBCL. Disorder diagnosis and decreasing left lateral amygdala nuclei volume significantly predicted total anxiety and depression scores in children with ASD ($p=0.04$) and ADHD ($p=0.025$). Anxiety and depression scores were significantly predicted by increasing right central amygdala nuclei volumes for all clinical groups ($p<0.05$), but not for typically-developing children. Increasing right central nuclei volumes also significantly predicted CBCL anxiety scores for all disorder categories. These results demonstrate that amygdala subnuclei volumes show varying developmental trajectories in children with neurodevelopmental disorders. Amygdala nuclei volumes may be potential biomarkers to differentiate neurodevelopmental disorders in high risk children. These methods may be used to identify children who would

benefit from targeted behavioral interventions to address anxiety and depression behaviors, and to assess the effects of such interventions in these groups of children.

Disclosures: D. Seguin: None. **J. Chen:** None. **J. Martinez-Trujillo:** None. **R. Nicolson:** None. **E.G. Duerden:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.16/A39

Topic: A.07. Developmental Disorders

Support: NIH Grant P50MH096891
University of Iowa Carver Chair

Title: Behavioral deficits and rescue in the Protocadherin 10 (Pcdh10) mouse model relevant to autism

Authors: *S. L. FERRI[1], E. S. BRODKIN[2], T. ABEL[1];
[1]Iowa Neurosci. Inst., Univ. of Iowa, Iowa City, IA; [2]Psychiatry, Univ. of PA Sch. of Med., Philadelphia, PA

Abstract: Protocadherin10 (Pcdh10) is a member of the cadherin superfamily and a nonclustered protocadherin. The activity-dependent cell adhesion molecule is highly expressed in the amygdala, striatum, and cerebellum, and is involved in the formation and elimination of dendritic spines and the guidance of thalamocortical projections. It has been linked to Autism Spectrum Disorder (ASD), a neurodevelopmental disorder that causes a number of symptoms, including impairments in social behavior and cognition. ASD affects four times as many males as females. Our group has previously reported male-specific deficits in social behavior and fear memory in mice heterozygous for a deletion of *Pcdh10* ($Pcdh10^{+/-}$), as well as increased spine density and decreased expression of NMDAR in the basolateral amygdala (BLA). Additionally, social behavior was rescued by systemic administration of the NMDAR partial agonist d-cycloserine. Currently, we are using a new transgenic mouse line with the Pcdh10 gene flanked by *loxP* sites in combination with a fast-expressing helper-dependent Cre-expressing virus to determine the effects of ablation of Pcdh10 in specific cell types and brain areas. In addition, preliminary data suggests that male $Pcdh10^{+/-}$ mice have decreased expression of the estrogen receptors alpha and beta, which may contribute to the sex differences observed. Future studies will focus on functional activity in the BLA and mechanisms underlying sex-specificity and behavioral rescue.

Disclosures: S.L. Ferri: None. **E.S. Brodkin:** None. **T. Abel:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.17/A40

Topic: A.07. Developmental Disorders

Support: Simons Foundation Autism Research Initiative (SFARI) grant 345034
Carver Chair in Neuroscience

Title: Sex specific involvement of indirect pathway medium spiny neurons in behavioral alteration of 16p11.2 hemi-deletion mouse model

Authors: *J. KIM[1], C. C. ANGELAKOS[2], J. F. LYNCH[2], S. L. FERRI[1], T. ABEL[1];
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Abstract: One of most common genetic variations found in autism spectrum disorder (ASD) is 16p11.2 deletion syndrome. Patients with this deletion usually display developmental delay and intellectual disability, including at least some features of ASD. Moreover, Attention-Deficit/Hyperactivity Disorder (ADHD) is commonly reported in the patients. Because the 16p11.2 chromosomal region in humans is highly conserved in mice, 16p11.2 deletion mouse model is considered a faithful model. Using the mouse model, we previously showed both male and female 16p11.2 hemi-deletion mice display hyperactive behavior compared to wild type sex-matched control mice. Because the striatum is the input structure of the basal ganglia, the key neural substrates for motor control, the present study examined the role of medium spiny neurons (MSNs), the major type of neuron in the striatum, in hyperactivity in 16p11.2 mouse model. MSNs can be characterized by their projections as either direct-pathway or indirect-pathway. The direct-pathway MSNs express dopamine receptor 1 and project to the SNr/GPi directly. The indirect-pathway MSNs express dopamine receptor 2 as well as adenosine receptor 2a (A2A) and extend their projections primarily to the GPe. We hypothesized that the medium spiny neurons play an important role in behavioral alteration of 16p11.2 hemi-deletion mouse model. To identify the importance of indirect-pathway MSNs, we crossed 16p11.2 flox mice to the A2A-CRE mice to produce A2A-CREx16p11.2 flox mice that lack genes of the 16p11.2 region in MSNs expressing dopamine receptor 2. Interestingly, male A2A-CREx16p11.2 flox mice showed hyperactivity compared to sex matched control group, suggesting the importance of indirect-pathway MSN. However, female A2A-CREx16p11.2 flox mice did not show the hyperactivity. These results imply the possibility that two different types of MSNs are involved in a sex-dependent manner in behavioral alteration in the 16p11.2 mouse model. We are currently assessing the role of direct-pathway MSNs using a similar approach.

Disclosures: **J. Kim:** None. **C.C. Angelakos:** None. **J.F. Lynch:** None. **S.L. Ferri:** None. **T. Abel:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.18/A41

Topic: A.07. Developmental Disorders

Title: Subconvulsive stimulation in early postnatal life produces sex-related differences in stereotypic behavior, mood, and the seizure threshold during the juvenile period

Authors: *B. A. KAHEN[1], J. VELISKOVA[1], L. VELISEK[1], L. K. FRIEDMAN[2];
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Abstract: Previously we observed that subconvulsive treatment in early postnatal life leads to sex-related autistic traits during the juvenile period including aberrant changes in handling, memory and social behavior. We hypothesized that immature males are more susceptible to behavioral deficits and alterations in the seizure threshold following sustained subconvulsive activity. To elevate glutamate levels and neuronal activity in early life without elicitation of seizures, low step-up doses of kainic acid (KA) were administered daily to male and female rat pups for 15 days beginning on postnatal day 6. Behavioral tests included the spontaneous alternating T-maze and forced swim test (FST). Latency to seizures was tested 24h after the last subconvulsive treatment with flurothyl or by a single convulsive dose of systemic KA administration. Brains were evaluated with Nissl staining. In the spontaneous alternating T-Maze, control groups, ASD males and females had more entries into the left arm but with similar spontaneous alteration rates and decision time. At 24 h after KA-induced status epilepticus, spontaneous alteration rates decreased; directional preference switched to the right arm. A marked reduction in decision time was noted for convulsive groups. In the forced swim test, control females traveled a greater distance with higher mobility and faster mean speed than males but less so after subconvulsive treatment. In Trial 2, decreased immobility was observed in ASD males compared to controls and ASD females. After administering the convulsive dose of KA, there was delayed onset to wet dog shakes and fore limb clonus in ASD males with fewer episodes. When flurothyl was administered, control males had faster onset to twitches and clonic seizures than females. After subseizure treatment, no sex-related differences were observed. Subconvulsive treatment, revealed no histological injury within the hippocampus or other brain regions unlike juvenile pups undergoing KA-induced status epilepticus. The marked reduction in the rate of spontaneous alteration and switching directional preference after convulsive seizures is likely due to hippocampal injury whereas, delayed onset to KA induced status epilepticus in the ASD group may be due to desensitization of KA receptors by our ASD protocol.

Subconvulsive treatment removed the sex difference associated with flurothyl suggesting the forebrain and not the brain stem are responsible for the alterations in the seizure threshold. The FST showed that juvenile control animals of both sexes were less mobile than the ASD groups suggesting subseizure activity increases anxiety but reduces behavioral despair.

Disclosures: B.A. Kahen: None. **J. Veliskova:** None. **L. Velisek:** None. **L.K. Friedman:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.19/A42

Topic: A.07. Developmental Disorders

Title: Postnatal subconvulsive activity selectively reduces NeuN antigenicity and polyphosphoinositide hydrolysis within limbic structures of juvenile rats

Authors: *L. K. FRIEDMAN[1], B. A. KAHEN[1], J. VELISKOVA[1], L. DI MENNA[2], F. NICOLETTI[3], L. VELISEK[1];
[1]Cell Biol. & Anat., New York Med. Col., Valhalla, NY; [2]IRCCS Neuromed, Molecular Neuropharmacology, Italy; [3]Physiol. and Pharmacol., Univ. Sapienza, Roma, Italy

Abstract: Previously we observed that subconvulsive treatment in early postnatal life leads to autistic traits including impairments in handling, memory and social behavior during the juvenile period. Group-I metabotropic glutamate (mGlu) receptors, such as the mGlu5 receptor subtype, play an important role in learning and memory suggesting that positive allosteric modulators (PAMs) may improve cognitive impairment associated with autism spectrum disorder (ASD). To elevate early life neuronal activity without elicitation of seizures, micromolar doses of kainic acid (KA) were administered to rat pups for 15 days beginning on postnatal day 6. The seizure threshold was subsequently tested with flurothyl. Pups were treated with LiCl (80 mg/kg) ± the mGlu5 receptor PAM, VU0360172 (10 mg/kg), 1 h prior to sacrifice. Dissected brain regions were used to measure inositolmonophosphate (InsP) formation, an indicator of polyphosphoinositde (PI) hydrolysis. Endogenous IsnP levels were measured by ELISA. Brains were histologically evaluated with NeuN, parvalbumin (PV), and Nissl stain. When flurothyl was administered, control males had faster onset to twitches and clonic seizures than females. After subseizure treatment, no sex-related differences were observed. Basal, unstimulated PI hydrolysis was reduced in the medial prefrontal cortex, thalamus, and amygdala following the subconvulsive treatment which was reversed by flurothyl administration. The mGlu5 receptor PAM did not enhance PI hydrolysis because of the subthreshold dose of the VU compound, except for in the thalamus suggesting that induction of seizures in pups sensitized with low doses of KA enhances mGlu5 receptor signaling in this region. Decreased basal PI hydrolysis, which

reduces mobilization of intracellular Ca^{2+}, was associated with selective loss of NeuN antigenicity (in the absence of cell loss) in the medial prefrontal cortex and amygdala. PV immunolabeling was preserved in the hippocampus, but significantly reduced in the amygdala. It appears that metabolism of the extra-hippocampal loop is predominantly affected by subtle but steady release of glutamate triggered by the ASD protocol. Loss of metabolic activity in critical brain regions could be responsible for deficits previously observed in the two-object recognition memory test and social interaction environments. We propose that PI hydrolysis is defective in the medial prefrontal cortex, thalamus, and amygdala regions in our model of ASD and is not rescued by pharmacological activation of mGlu5 receptors. Instead, mGlu5 potentiation with PAMs to improve cognition may be a more effective treatment strategy for children with epilepsy.

Disclosures: L.K. Friedman: None. **B.A. Kahen:** None. **J. Veliskova:** None. **L. Di Menna:** None. **F. Nicoletti:** None. **L. Velisek:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.20/A43

Topic: A.07. Developmental Disorders

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Wellcome Trust Senior Clinical Research Fellowship, 100227

Title: A neuroanatomical basis linking perceptual inflexibility to cognitive rigidity in autism

Authors: *T. WATANABE[1,2], R. P. LAWSON[3,4], Y. S. E. WALLDÉN[4], G. E. REES[2,4];
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Abstract: Behavioural studies have reported high perceptual stability in individuals with autism spectrum disorder (ASD). However, neural mechanisms by which such sensory-related symptoms can coexist and often correlate with seemingly independent core symptoms of the condition remain unknown. Here, we have identified such a key neuroanatomical substrate in high-functioning adults with autism. First, we assessed perceptual stability using a test of

bistable visual perception with a structure-from-motion stimulus, and quantified cognitive rigidity by a spontaneous task-switching test. By comparing behavioural responses to these tests, we found that over-stable visual perception of individuals with autism is linked with their cognitive rigidity, which in turn is associated with core restricted, repetitive behaviours symptoms. Measuring grey matter volume with MRI, we next found that both perceptual and cognitive inflexibility were correlated with a smaller grey matter volume in the posterior superior parietal lobule (pSPL) in participants with ASD. Moreover, a non-parametric mediation analysis suggested that the pSPL is a mediator linking perceptual stability to cognitive rigidity. Furthermore, a structural equation modelling analysis indicated the possibility that, in both individuals with ASD and neurotypical controls, this region could be related to domain-general behavioural/mental flexibility. These findings uncover a key neuroanatomical mediator of the perceptual and cognitive inflexibility in autism and open up the possibility of future studies on how the core symptoms of this spectrum interact with characteristic features of sensory perception.

Disclosures: T. Watanabe: None. **R.P. Lawson:** None. **Y.S.E. Walldén:** None. **G.E. Rees:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.21/A44

Topic: A.07. Developmental Disorders

Support: NIH COBRE PG20GM103650

Title: Evidence of wide spread white matter compromise in children and adults with autism: A large scale diffusion imaging study using the ABIDE II repository

Authors: *S. R. OTTO, L. M. RAY, J. A. TRAVERS, I. BRUKETTA, M. L. MONTERO, J. J. HUTSLER, S. M. HAIGH;
Psychology, Univ. of Nevada, Reno, Reno, NV

Abstract: Autism Spectrum Disorder (ASD) is characterized by a variety of abnormal behaviors ranging from difficulties in social communication to heightened sensory processing. One potential mechanism that can explain how these disparate behaviors are related is alterations to white matter connectivity. Disturbances to the underlying white matter in ASD may lead to impaired functional processing between distributed neural networks. Previous studies using diffusion magnetic resonance imaging (dMRI) have consistently reported findings of white matter disruption in ASD, however the results from many of these studies are often limited by small sample sizes and are frequently conducted on children, despite little being known about the

developmental trajectory of white matter tracts. The findings from the few studies in adults with ASD do not provide conclusive evidence as to whether white matter tracts are abnormal are not. The present study aimed to investigate whether there is evidence of abnormal white matter connectivity in ASD across a large sample of subjects in adults with ASD compared to a pediatric population. Diffusion MRI data was acquired from the Autism Brain Imaging Data Exchange II, which is an international neuroimaging data-sharing initiative to promote discovery science on the brain connectome in ASD. In addition, we acquired dMRI data from research groups both at Carnegie Mellon University and the University of Pittsburgh. In total, we analyzed 335 subjects (186 ASD, 149 NT), with 156 subjects in the pediatric group (96 ASD, 60 NT; ages 7-17 years old) and 179 in the adult group (90 ASD, 89 NT; ages 18-64 years old). Control subjects were matched on age, gender and IQ. All data were collected on a 3-Tesla scanner. Tract Based Spatial Statistics (TBSS) was performed using FMRIB's FSL software. TBSS analyses revealed decreased FA in the ASD pediatric group and in the adult ASD group compared to NT controls. The findings in the pediatric group were evident in nearly all white matter tracts in the brain. Interestingly, FA reductions in the ASD adult group were less wide spread compared to the ASD pediatric group. Together, these results show that white matter integrity is more compromised in ASD and the reduced integrity persists throughout adulthood. These findings highlight the need for longitudinal studies on the impact of white matter integrity throughout adolescence and into adulthood, and the impact it has on behavioral functioning in ASD.

Disclosures: S.R. Otto: None. **L.M. Ray:** None. **J.A. Travers:** None. **I. Bruketta:** None. **M.L. Montero:** None. **J.J. Hutsler:** None. **S.M. Haigh:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.22/A45

Topic: A.07. Developmental Disorders

Support: NIH Grant R01MH110630

Title: Lack of replication of case-control differences in functional connectivity in ASD across multiple sites

Authors: *Y. HE, L. BYRGE, D. P. KENNEDY;
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Abstract: Studies on Autism Spectrum Disorder (ASD) have been increasingly using resting-state functional Magnetic Resonance Imaging (rs-fMRI) to investigate alterations of functional connectivity. While findings have the potential to advance our knowledge about the

neuropathology of ASD, largely inconsistent results across studies have hampered the identification of clinical biomarkers or neural mechanisms underlying ASD. In this study, we investigated two factors -- denoising methods and site effects -- that could influence the replicability of functional connectivity. We analyzed rs-fMRI data of four independently acquired datasets (each including ASD and control participants) from the Autism Brain Imaging Data Exchange (ABIDE-I and II), using 31 different denoising strategies. We evaluated the replicability of group-average functional connectome and group-comparison differences in functional connectivity. Within datasets, both group-average functional connectomes and group-differences were consistent across different denoising pipelines (r = .80-1.0 / r = .55-0.99), with the largest disparity dependent on whether global signal regression (GSR) was used or not. However, across sites, while group-average connectomes were highly consistent (r = .82-.89), the consistency of group-differences was dramatically low (r = -.02-.16) regardless of denoising pipelines, even when comparing groups at a large-scale network level (relative to a fine edge level). These results indicate that case-control differences in functional connectivity could not be replicated across multiple sites, even when using the same denoising pipeline. As there are other methodological factors that potentially influence across-site replication (e.g., scanner-related differences, subject or cohort differences, post-processing analyses, the true effect size of ASD alterations), current results cannot rule out the possibility of replicable differences of functional connectivity existing in ASD. However, they do highlight the importance of examining replicability in future studies of ASD, and, more generally, call for extra caution when describing and interpreting alterations in functional connectivity across groups of individuals.

Disclosures: **Y. He:** None. **L. Byrge:** None. **D.P. Kennedy:** None.

Poster

458. Autism: Physiology, Systems, and Behavior

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 458.23/A46

Topic: A.07. Developmental Disorders

Support: UW2020 Pilot Award
R25 Team-Science

Title: Maternal sleep disordered breathing during pregnancy induces behavioral and synaptic aberrations in the offspring: Potential implications for autism spectrum disorders

Authors: *A. M. VANDERPLOW, B. A. KERMATH, A. C. EWALD, S. M. JOHNSON, T. L. BAKER, J. J. WATTERS, M. CAHILL;
Comparative Biosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: Sleep disordered breathing (SDB) is characterized by recurring breathing cessations during sleep, causing intermittent hypoxia (oxygen deprivation) often several hundred times per night. SDB is present in ~15% of pregnant women as compared to ~2-4% of non-pregnant women of childbearing age. Risk factors for gestational SDB development bear striking similarities to the collection of maternal risk factors for autism spectrum disorders (ASD), including advanced maternal age and maternal obesity. Maternal immune activation/inflammation is both a consequence of SDB, and an independent risk factor for, ASD. We posit that an overlooked, yet increasingly common inflammatory stimulus, maternal SDB, contributes to ASD etiology. We recently developed a rat model in which to study the consequences of maternal SDB on the offspring by exposing pregnant rats to nightly intermittent hypoxia from gestational days 10-21. Our findings indicate that offspring of mothers subjected to intermittent hypoxia during pregnancy exhibit deficits in several autism-relevant behaviors, including a constellation of cognitive impairments, reduced interest in social interaction, and heightened anxiety. In most instances, the magnitude of behavioral disruption was more severe in male than female offspring. To begin to understand the mechanisms contributing to these behavioral aberrations, we examined the density of dendritic spines in the prefrontal cortex and found that offspring of mothers subjected to nightly intermittent hypoxia exhibited a striking increase in dendritic spine density as compared to control offspring. Similar to our behavioral observations, dendritic spine aberrations were more prominent in male vs. female offspring. Taken together, these findings indicate that maternal sleep disordered breathing not only induces autism-relevant behavioral impairments, but also mimics the heightened cortical synaptic connectivity phenotypes recently uncovered in autism. Future studies are aimed at identifying a role for microglial inflammation and concomitant reduction in microglial-mediated synaptic pruning in the behavioral and synaptic structural alterations that we have revealed in this model.

Disclosures: **A.M. Vanderplow:** None. **B.A. Kermath:** None. **A.C. Ewald:** None. **S.M. Johnson:** None. **T.L. Baker:** None. **J.J. Watters:** None. **M. Cahill:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.01/A47

Topic: A.07. Developmental Disorders

Support: Jiangsu Outstanding Young Investigator Program(BK20160044 and BK20160047)
the National Natural Science Foundation of China (grant 81471301)
the National Key Research and Development Program of China (2016YFC1306703)

Title: Using human HPSC-derived cerebral organoid to model deficits of cortical neurogenesis in Down syndrome

Authors: *X. TANG[1], L. XU[1], Y. HONG[1], M. XU[1], Y. HU[1], Y. LIU[2];
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Abstract: Down syndrome (DS), caused by trisomy of chromosome21, approximately occurs in 1 of every 800 live births. Alterations in brain growth during early cortical development process are thought to underlie the cognitive impairments in DS, but its mechanism remains unknown. Here, we employed patient iPS-derived cerebral organoids to investigate pathological abnormalities associated with DS. Our results revealed that DS-derived cerebral organoids showed a reduction in number of cortical neurons in IV and II layers, which is associated with diminished proliferation of progenitors in VZ-like region. By whole-transcriptome analysis, we found neurogenesis-related pathway were altered in DS. Furthermore, correction of DSCAM gene and its downstream PAK1 pathway reverse the abnormal neurogenesis in DS. Our data suggest that impaired proliferation in DS apical progenitors as well as defective neurogenesis may contribute to the reduced cortical thickness of DS patients, and emphasize the role of DSCAM and PAK1 in regulating the cortical development, which provide the basis for prenatal therapeutic interventions in DS.

Disclosures: X. Tang: None. **L. Xu:** None. **Y. Hong:** None. **M. Xu:** None. **Y. Hu:** None. **Y. Liu:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.02/A48

Topic: A.07. Developmental Disorders

Support: TCP15021

Title: Discovery and characterization of novel selective NKCC1 inhibitors for down syndrome, autism and brain disorders with depolarizing GABAergic transmission

Authors: *A. SAVARDI[1], M. BORGOGNO[2], R. NARDUCCI[1], G. LA SALA[2], J. ORTEGA[2], M. SUMMA[3], R. BERTORELLI[3], A. ARMIROTTI[4], A. CONTESTABILE[1], M. DE VIVO[2], L. CANCEDDA[1,5];
[1]Local Micro-environment and Brain Develop. Lab., [2]Mol. Modeling and Drug Discovery Lab., [3]In Vivo Pharmacol. Facility, [4]Analytical Chem. Facility, Fondazione Inst. Italiano Di Tecnologia, Genova, Italy; [5]Dulbecco Telethon Inst., Rome, Italy

Abstract: Proper GABAergic transmission through Cl-permeable $GABA_A$ receptors is fundamental for physiological brain development and function. Indeed, defective GABAergic signaling -due to a high ratio of expression of the Cl importer NKCC1 and Cl exporter KCC2- has been implicated in several neurodevelopmental disorders, including Down syndrome (DS). Interestingly, NKCC1 inhibition by the FDA-approved diuretic bumetanide reverts cognitive deficits in the TS65Dn mouse models of DS and core symptoms of other brain disorders (e.g., autism) in a number of rodent models and/or clinical trials. However, the required chronic treatment with bumetanide is burdened by its diuretic side effects caused by the antagonism of the kidney Cl^- importer NKCC2, which leads to hypokalemia and jeopardizes drug compliance. Crucially, these issues would be solved by selective NKCC1 inhibitors, thus devoid of the diuretic effect. Starting from bumetanide's structure, we applied a computational ligand-based approach to design new molecular entities that we tested *in vitro* for their capacity to selectively block NKCC1. Among the 3 newly-identified and highly promising NKCC1 inhibitors, one showed excellent solubility and metabolic stability *in vitro.* Moreover, analysis of WT and Ts65Dn mice systemically treated with this NKCC1 inhibitor revealed no diuretic effect. Finally, chronic treatment with our novel, selective NKCC1 inhibitor was able to rescue cognitive deficits in Ts65Dn mice in four different memory tasks, and social impairments in a mouse model of autism, with no major signs of toxicity. Thus, our selective NKCC1 inhibitor devoid of the diuretic effect could represent a suitable and solid therapeutic strategy for the treatment of Down syndrome, autism and all the brain disorders with depolarizing GABAergic transmission.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.03/A49

Topic: A.07. Developmental Disorders

Title: Early pharmacological treatment with bumetanide rescues cognitive impairment and increased susceptibility to seizures in the Ts65Dn mouse model of Down syndrome

Authors: *I. ZIOGAS[1,2], M. PARRINI[1], A. CONTESTABILE[1], L. CANCEDDA[1,3];
[1]Inst. Italiano Di Tecnologia, Genova, Italy; [2]Univ. Degli Studi di Genova, Genova, Italy; [3]Dulbecco Telethon Inst., Rome, Italy

Abstract: Down syndrome (DS) is the leading cause of genetically-defined intellectual disability. Additionally, DS individuals often present with increased susceptibility to epileptic seizures and hyperactivity. Recently, several studies identified altered GABAergic activity

trough chloride-permeable $GABA_A$ receptors as one of the main contributors to impaired cognitive performance in the Ts65Dn mouse model of DS. Data from adult Ts65Dn mice and DS individuals showed an increased expression of the chloride importer NKCC1. As a result, intracellular chloride concentration is higher in Ts65Dn mice and GABAergic responses are depolarizing (rather than hyperpolarizing and inhibitory). Accordingly, treatment with the FDA-approved diuretic and NKCC1 inhibitor bumetanide during adulthood, rescues inhibitory GABAergic transmission and cognitive deficits in DS mice, although the beneficial effect of the treatment is rapidly lost upon drug withdrawal. However, hyperactivity and susceptibility to seizures are not rescued by bumetanide treatment in adulthood. Here, we investigated the long-lasting effects of an early bumetanide administration during the first 2 weeks of development on cognitive performance, seizure susceptibility and hyperactivity in Ts65Dn mice. We found a rescue in long-term memory as assessed by the novel object recognition and contextual fear conditioning tests in adult animals. Moreover, early bumetanide treatment also rescued susceptibility to seizures in adult Ts65Dn mice. Finally, since bumetanide treatment of human infants can lead to deafness, we assessed ototoxicity in adult WT and Ts65Dn mice treated in early development and found no significant deficits in acoustic startle-response. Currently, we are assessing the impact on hyperactivity in adulthood and the mechanisms underlying the long-lasting behavioral effects of early bumetanide administration at the molecular and circuit levels. Our results suggest that time-specific intervention possibly impacting on the trajectories of the developing brain could rescue cognitive performance and deficits that are not rescued by treatment in adulthood, avoiding the adverse diuretic effects of a lifetime treatment.

Disclosures: I. Ziogas: None. **M. Parrini:** None. **A. Contestabile:** None. **L. Cancedda:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

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Topic: A.07. Developmental Disorders

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Alzheimer's Association grant NIRG-15-362799
BrightFocus Foundation grant A2017457S

Title: Genetic reduction of eEF2K ameliorates memory deficits and synaptic failure in a mouse model of Down syndrome

Authors: *X. WANG[1], Q. YANG[2], T. MA[3];
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Salem, NC; [2]Intrnl. Med. - Gerontology and Geriatric Med., WFU Hlth. Sci., Winston Salem, NC; [3]Intrnl. Medicine-Geriatrics, Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Down syndrome (DS) is one of the most common forms of intellectual disability that is caused by trisomic repeat of chromosome 21. Later in their life, individuals with DS usually develop brain pathology and dementia syndrome typical of Alzheimer's disease (AD). Previous studies have shown that synaptic failure is a key pathophysiology for both AD and DS. *De novo* protein synthesis is essential for memory formation and synaptic plasticity, and recent studies indicate a critical role of impaired *de novo* protein synthesis in AD pathogenesis. Here we explored the role of eukaryotic elongation factor 2 (eEF2) in Down syndrome. eEF2 is a part of the ribosome machinery and facilitates transfer of tRNA from A site to P site, thus plays important role in protein synthesis. eEF2 can be phosphorylated and deactivated by the only known kinase eEF2K, resulting in inhibition of general protein synthesis. We crossed eEF2K+/- mice to Ts65Dn DS model mice, generating four genotypes: WT, eEF2K+/-, Ts65Dn, and Ts65Dn/eEF2K+/-. Multiple behavioral tasks were performed to evaluate learning and memory including: novel object recognition, hidden platform Morris water maze, and passive avoidance. In brief, our data suggest that DS-associated memory deficits were ameliorated by repressing eEF2K, as indicated by improved performance in Ts65Dn/eEF2K+/- mice compared to that of Ts65Dn mice. Electrophysiological study showed that long-term potentiation (LTP) failure in Ts65Dn mice was alleviated by knocking down eEF2K. Taken together, these data suggest that genetic reduction of eEF2K can ameliorate memory deficits and synaptic failure in a mouse model of Down syndrome. Our findings thus provide insights into a potential therapeutic target for the treatment of cognition impairments in Down syndrome.

Disclosures: **X. Wang:** None. **Q. Yang:** None. **T. Ma:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.05/A51

Topic: A.07. Developmental Disorders

Title: Pharmacological modulation of intracellular chloride concentration restores GABA mediated inhibition in down syndrome neuronal networks

Authors: *I. COLOMBI, M. ALBERTI, M. CHIAPPALONE, A. CONTESTABILE, L. CANCEDDA;
Fondazione Inst. Italiano Di Tecnologia, Genova, Italy

Abstract: Down syndrome (DS) is a genetic disorder that causes intellectual disability in children and adults. Altered GABAergic signaling through chloride-permeable GABAA

receptors (GABAARs) has been shown to play a major role in brain dysfunction and cognitive impairment in the Ts65Dn mouse model of DS. In particular, higher intracellular chloride concentration ([Cl-]i) due to increased expression of the chloride importer NKCC1 alters synaptic inhibitory/excitatory balance in neurons. In fact, treatment of Ts65Dn mice with the FDA-approved NKCC1 inhibitor Bumetanide restored the [Cl-]i to value comparable with wild-type (WT) mice and rescued both inhibitory GABAergic signaling and hippocampus-dependent memory in adult mice. However, the effect of the pharmacological treatment on neuronal network dynamics has never been directly studied in DS. To this aim, we used primary hippocampal cultures and acute brain slices from Ts65Dn and WT mice coupled to Microelectrodes Array technology (MEA) to evaluate the efficacy of the pharmacological treatments with Bumetanide in restoring inhibitory GABAergic transmission in Ts65Dn neuronal networks. We found that Ts65Dn cultures and slices exhibited alterations in network dynamics and GABAergic inhibition. Moreover, the application of Bumetanide restored the normal inhibitory action of GABA in Ts65Dn cultures and slices. Our findings indicate that MEA recordings coupled to neuronal networks could be used to predict the effectiveness of new therapies in pathologies that exhibit alterations of GABAergic inhibition, such as neurodevelopmental disorders and autism.

Disclosures: I. Colombi: None. **M. Alberti:** None. **M. Chiappalone:** None. **A. Contestabile:** None. **L. Cancedda:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.06/A52

Topic: A.07. Developmental Disorders

Support: NIH-NICHD (1R21HD085288-01)
NIH-NICHD (U54 HD090256)
Wisconsin Alumni Research Fund
University of Wisconsin School of Medicine and Public Health

Title: Gene expression analysis of dorsal and ventral cortical progenitors from Down syndrome iPSC models

Authors: *J. L. MARTINEZ[1,2], C. L. SIROIS[2], Y. GIFFIN-RAO[2], A. BHATTACHARYYA[3,2]; [1]Cell. and Mol. Biol. Program, Univ. of Wisconsin-Madison, Madison, WI; [2]Waisman Ctr., [3]Cell. and Regenerative Biol., Univ. of Wisconsin, Madison, WI

Abstract: Down Syndrome (DS), or trisomy 21, is a complex brain disorder that leads to altered cortical development resulting in intellectual impairment. Affecting one in every 700 babies born

in the U.S., DS is the most common genetic form of intellectual disability. It is estimated that there are more than 400,000 people living with DS in the U.S. However, our understanding of how this extra human chromosome 21 (HSA21) contributes to the altered neural development remains unknown. Our study uses human pluripotent stem cells (hPSC) that carry the trisomy 21 mutation to study the underlying mechanisms of DS neuropathophysiology. The process of neuroepithelial differentiation from hPSCs resembles *in vivo* cortical development in temporal course, morphogenesis and biochemical changes. Using this model, we aim to define the intrinsic differences in DS cortical development that may lead to the characteristic intellectual impairment.
Isogenic trisomy 21 and control iPSCs were differentiated to dorsal or ventral cortical progenitors following established protocols. The cells were harvested at Day 17 and gene expression was analyzed using RNASeq, resulting in four comparative groups; DS Ventral, DS Dorsal, Control Ventral and Control Dorsal. Principal component analysis (PCA) showed that ventral and dorsal patterning was the greatest source of variance (69% for patterning vs 20% for genotype). This high variance validated the dorsal versus ventral patterning of the cells. Because of this high variance, we focused our analysis on ventral and dorsal differentiation independent of one another. PCA results between DS Ventral/Control Ventral and DS Dorsal/Control Dorsal showed clear clustering based on the genetic mutation (80% and 66% respectively). Further gene expression analysis showed over 2,000 differentially expressed genes in ventral DS versus Control and over 1,000 differentially expressed genes in dorsal DS versus Control, all with padj values <0.01. Of these differentially expressed genes, 36 of the ventral genes and 45 of the dorsal genes are encoded on HSA21. We focused our analysis on differential expression amongst genes with a padj <0.01 and a log2Fold change greater than 5, which resulted in 25 and 28 genes of interest for ventral and dorsal respectively. This comprehensive analysis defines gene expression changes due to trisomy 21 in two different cortical lineages. Thus, this study highlights potential target genes for further pathway and expression analysis in an ongoing effort to understand the mechanisms underlying DS intellectual disability.

Disclosures: **J.L. Martinez:** None. **C.L. Sirois:** None. **Y. Giffin-Rao:** None. **A. Bhattacharyya:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.07/A53

Topic: A.07. Developmental Disorders

Support: Indiana Clinical and Translational Sciences Institute funded, in part by Grant Number UL1TR001108 from the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award

Department of Psychology, Indiana University Purdue University Indianapolis

Title: Non-linear developmental overexpression of DYRK1A in the Down syndrome brain—A paradigm shift in gene dosage imbalance

Authors: *L. E. HAWLEY[1], R. ROPER[1], C. R. GOODLETT[2];
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Abstract: Down syndrome (DS) is caused by trisomy of human chromosome 21 (Hsa21) and is the leading genetic cause of intellectual disability. Trisomy of Dual-specificity tyrosine-phosphorylated regulated kinase 1A (DYRK1A), found on Hsa21, has been linked to DS neurological deficits. The traditional model relating trisomy to DS-related brain phenotypes is that trisomic gene expression is upregulated by ~1.5-fold, corresponding to gene dosage in all brain tissues throughout development. There are no systematic studies in DS mouse models that assess the developmental regulation of DYRK1A protein expression across different brain regions. Using Western blot, we quantified DYRK1A at different ages over early postnatal development in the cerebellum, hippocampus, and cerebral cortex of Ts65Dn DS mice and found that trisomic expression (relative to euploid control) is increased an average of 4.5 fold on postnatal day ([P]6), declining to an average of 1.1 fold by the third postnatal week (P24). The trisomic cerebellum exhibited the highest elevation at P6 (>5-fold increase), corresponding to reduced cerebellar size and cellular density in DS mice at this age, suggesting that the structural deficit during this period of rapid development in the cerebellum may result from the non-linear amplification of DYRK1A. These data imply that trisomic *Dyrk1a* expression is developmentally regulated and interacts with one or more trisomic or disomic genes and is not simply a linear function of gene dosage at all ages and in all tissues. To test this hypothesis, we reduced *Dyrk1a* copy number at conception in both trisomic and euploid mice and quantified postnatal DYRK1A expression, with the prediction that reduced *Dyrk1a* copy number in otherwise trisomic animals would significantly reduce DYRK1A protein levels, but that the extent of reduction would be non-linear in trisomic animals depending on age and tissue. Our data indicate normalizing only *Dyrk1a* copy number in trisomic animals yielded highly variable levels of DYRK1A protein expression that depended on tissue type, even resulting in expression lower than euploid levels in some instances. In euploid mice, reducing *Dyrk1a* by one copy generally reduced DYRK1A expression by 50%, regardless of tissue type. The non-intuitive relationship between gene dosage and protein expression suggests more complex developmental regulation of DYRK1A beyond gene copy number. These data emphasize the need to understand the age-dependent regulation of antecedent conditions that are causing changes in *Dyrk1a* expression in the brain.

Disclosures: L.E. Hawley: None. **R. Roper:** None. **C.R. Goodlett:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

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Program #/Poster #: 459.08/A54

Topic: A.07. Developmental Disorders

Support: NIH-NICHD (1R21HD085288-01)
University of Wisconsin Madison, Sophomore Research Fellowship
NIH Grant (U54 HD090256)

Title: Investigating the abnormal expression of critical neurogenesis and gliogenesis control genes in trisomy 21 using iPSCs

Authors: *D. J. QUIRICONI[1], Y. TAO[2], S.-C. ZHANG[3], A. BHATTACHARYYA[4];
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Abstract: Trisomy 21, or Down Syndrome, is the most common genetic cause of intellectual disability, affecting about 1 in every 700 babies born. Individuals with trisomy 21 display several central nervous system (CNS) abnormalities, including decreased volume in several brain regions. In addition, a well-documented and prominent cellular abnormality in the CNS of individuals with trisomy 21 is a lower ratio of neurons to astrocytes relative to control individuals. A possible explanation for this disparity is a premature end of neuron generation and subsequently a premature shift to predominantly gliogenesis. To investigate this hypothesis, we used isogenic control and trisomy 21 iPSCs differentiated to neural progenitors to recapitulate early CNS development in vitro. We compared expression levels of critical neurogenesis and gliogenesis genes at 30, 50, and 60 days in vitro. Preliminary data demonstrates altered temporal expression patterns in trisomy 21 neural progenitors relative to controls. S100B, a glial gene, demonstrates constitutive overexpression, consistent with its location on chromosome 21. The expression of the neural progenitor transcription factor Pax6 is higher at earlier time points relative to controls, but expression decreases earlier. NFI-A, a transcription factor that controls the onset of gliogenesis, shows early overexpression. Data from fetal brain tissue showed similar overexpression of S100B and NFIA in trisomy 21 at the end of the early fetal period and beginning of early mid-fetal period. These results support the idea that abnormal expression of these established neurodevelopmental transcription factors, transcription regulators, and signaling proteins contribute to the atypical neuron:astrocyte ratio due to the premature onset of gliogenesis.

Disclosures: D.J. Quiriconi: None. **Y. Tao:** None. **S. Zhang:** None. **A. Bhattacharyya:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.09/A55

Topic: A.07. Developmental Disorders

Support: NIH NIA RF1 grant

Title: Systematic functional analysis of 21st chromosome genes using *C. elegans*

Authors: *J. PIERCE, S. M. SANCHEZ, S. NORDQUIST, S. R. SMITH;
Univ. of Texas at Austin, Austin, TX

Abstract: Down syndrome (DS), caused by trisomy of the 21st chromosome, leads to lifelong cognitive impairment. Efforts to understand this disorder first require an understanding of the genes encoded on the 21st chromosome (HSA21). While progress has been made using traditional mouse models, C. elegans represents a model complementary to uncovering the in vivo function of genes. Using RNAi and loss-of-function mutants, we systematically investigated the role of all HSA21 orthologs, excluding keratin-encoding genes, in viability and neuronal function. We identified ten HSA21 orthologs that are required for behavioral phenotypes. We also found that three of these genes are required for normal release of the neurotransmitter acetylcholine. This includes a known synaptic gene unc-26 (SYNJ1), as well as uncharacterized genes pdxk-1 (PDXK) and mtq-2 (N6ATM1). Furthermore, we found that the glutamine methyltransferase MTQ-2 localizes to cholinergic synapses where it appears to regulate neurotransmission via methylation of a Gα/o signaling protein. Going forward, we are overexpressing each of the HSA21 orthologs in worm and investigating which contribute to overexpression phenotypes, and which are subject to either direct or indirect forms of compensation. Differences in compensation could underlie the variable penetrance and expressivity in individuals with DS. As the first systematic functional analysis of HSA21 orthologs, our study may serve as a platform to understand genes that underlie phenotypes associated with DS.

Disclosures: **J. Pierce:** None. **S.M. Sanchez:** None. **S. Nordquist:** None. **S.R. Smith:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.10/A56

Topic: A.07. Developmental Disorders

Support: NIH Grant NS076708

Title: Activation of the integrated stress response underlies the behavioral and neurophysiological abnormalities in Down syndrome

Authors: *P. ZHU[1], S. KHATIWADA[1], Y. CUI[2], S. DOOLING[1], J. J. KIM[3], W. LI[2], P. WALTER[4], M. COSTA-MATTIOLI[1];
[1]Dept. of Neurosci., [2]Dept. of Mol. and Cell. Biol., [3]Stem Cells and Regenerative Med. Ctr., Baylor Col. of Med., Houston, TX; [4]Univ. of California at San Francisco, San Francisco, CA

Abstract: Little is known about the role of protein homeostasis networks in brain function. Using a mouse model of Down syndrome (DS), the most common genetic cause of intellectual disability in humans, we investigated the translational landscape in DS. We found that activation of the integrated stress response (ISR)—an evolutionarily conserved signaling network that maintains proteostasis by controlling protein synthesis—in the brain of DS mice and humans leads to a reduction in translation. Genetic and pharmacological inhibition of either the double-stranded RNA-activated protein kinase (PKR) branch of the ISR or the function of eIF2•eIF2B, where the ISR exerts its central control, reversed the enhanced inhibitory synaptic transmission as well as the deficits in long-term synaptic plasticity and memory in DS mice. Our findings unveil a crucial role for the ISR in DS pathophysiology and suggest tuning of the ISR as a promising therapeutic intervention for DS.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

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Topic: A.07. Developmental Disorders

Support: NIH R01 NS086933-02 (CAH)
Alzheimer's Association MNIRGDP-12-258900 (CAH)
Linda Crnic Institute (CAH)
LeJeune Foundation (CAH)
NIH T32 MH016880 (HW)

Title: RCAN1 overexpression and mitochondrial dysfunction

Authors: *H. WONG, J. LEVENGA, C. ARDIZZONE, C. HOEFFER;
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Abstract: *Regulator of Calcineurin 1 (RCAN1)* is a gene overexpressed in Down syndrome (DS) and regulates activity of the calcium/calmodulin-dependent phosphatase calcineurin (CaN), which is involved in many neuromolecular signaling pathways. DS is associated with neurodevelopmental defects and intellectual disability which may be linked to abnormal neural CaN activity. Additionally, because DS patients and DS model mice develop symptoms consistent with early onset Alzheimer's disease (AD), DS-linked genes such as *RCAN1* may also play a role in AD-related neurodegeneration. We found previously that brain-specific overexpression of a human RCAN1 isoform in mice promotes early age-dependent memory and synaptic plasticity deficits, tau pathology, and dysregulation of the CaN substrate dynamin-related protein 1 (DRP1) associated with mitochondrial dysfunction and oxidative stress, reproducing key DS and AD features. In the current study, we examine CaN signaling and mitochondrial function in the *Dp(16)1Yey/+* (Dp16) mouse model of DS with and without *Rcan1* gene dosage correction. This work should improve understanding about the molecular basis of neurological phenotypes and AD progression in DS and whether RCAN1 may be a therapeutic target for treatment.

Disclosures: H. Wong: None. **J. Levenga:** None. **C. Ardizzone:** None. **C. Hoeffer:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.12/A58

Topic: A.07. Developmental Disorders

Support: Arizona Alzheimer's Consortium
BrightFocus Foundation
NIH-NIA P01 AG014449
NIH-NIA R01 AG061566

Title: Cerebellar Purkinje cells alterations in demented and non-demented subjects with Down syndrome

Authors: *E. J. MUFSON, J. C. MIGUEL, S. E. PEREZ;
Barrow Neurolog. Inst., Phoenix, AZ

Abstract: Despite extensive brain beta amyloid (Aβ) plaque and tau containing neurofibrillary tangles (NFTs) in individuals with Down syndrome (DS), only two thirds develop dementia. In addition, cerebellar hypoplasia is another neuropathologic characteristic, which may underlie defects in fine motor learning in subjects with DS. Cerebellar Purkinje cells (PC) inhibit neurons that regulate motor movement by releasing gama-aminobutyric acid. PC are characterized by the presence of the low affinity $p75^{NTR}$ and high affinity TrkA cognate receptors for nerve growth factor as well as the calcium binding protein calbindin D-28K (Calb). The pathobiology of cerebellar PC in DS is an under investigated area. To gain greater insight in cerebellar cellular pathology we quantitated the number of PC immunoreactive for TrkA, $p75^{NTR}$ and Calb in sections obtained from cases with a clinical diagnosis of DS without dementia (DSD-), DS with dementia (DSD+), Alzheimer's disease (AD) and non-demented controls (ND) by combining imunohistochemistry and densitometry. Plaque load was measured using antibodies against amyloid precursor protein APP/Aβ (6E10), Aβ42 and Aβ40. Counts revealed that the number of TrkA positive PC neurons were significantly lower in AD compared to ND controls, but not in DSD- or DSD+. However, $p75^{NTR}$ positive PC counts were reduced in DSD+ and AD compared to ND cases. Of the two amyloid peptides, Aβ42 but not Aβ40 was present in the cerebellum of both DS groups and AD. Both DSD+ and DSD- had higher Aβ42 plaque loads in the cerebellar molecular layer compared to ND controls. We found a correlation between Aβ42 and APP/Aβ plaque loads (P<0.001). Counts of Calb positive PC were highly correlated with optical density (OD) measurements for Calb and the number of $p75^{NTR}$ PC (P<0.001), but not with the number of TrkA positive PC across groups. Counts of $p75^{NTR}$ positive PC neurons correlated with both $p75^{NTR}$ OD and numbers of Trk A positive PC. There were also correlations between the OD of Calb and $p75^{NTR}$ positive PC and their dendritic fields, respectively (P<0.01). The data indicate a differential dysregulation between $p75^{NTR}$ and TrkA in cerebellar PC, which may contribute to the cognitive and motor deficits seen in DS.

Disclosures: E.J. Mufson: None. **J.C. Miguel:** None. **S.E. Perez:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.13/A59

Topic: A.07. Developmental Disorders

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ALANA USA Foundation
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Awakening Angels Foundation

Title: Behavioral and electrophysiological assessments of the Ts65Dn mouse model of Down syndrome

Authors: *D. B. VICTORINO[1,2], J. J. SCOTT-MCKEAN[2], S. BAKER[2], C. A. SCORZA[1], A. C. S. COSTA[2,3];
[1]Dept. of Neurol. and Neurosurg., Univ. Federal de Sao Paulo, Sao Paulo, Brazil; [2]Dept. of Pediatrics, [3]Dept. of Psychiatry, Case Western Reserve Univ., Cleveland, OH

Abstract: Down syndrome (DS) is the most frequent cause of genetically defined intellectual disability, and results from the presence of an extra copy of chromosome 21. A wide range of neurological phenotypes is typically observed in persons with DS, including increased incidence of seizure and anxiety disorders. Mouse models of DS, particularly Ts65Dn mice, represent important tools for studying and understanding the pathophysiology of DS co-morbidities. As a model of trisomy 21, Ts65Dn mice exhibit several DS-like phenotypes, including impaired synaptic plasticity. It has been proposed recently that the hippocampus of Ts65Dn mice shows an intracellular accumulation of chloride, which leads to the reversal of GABA type-A receptor ($GABA_AR$) responses from inhibitory to excitatory. In this context, positive allosteric modulators of $GABA_AR$ might produce paradoxical effects that might aggravate rather than ameliorate pre-existing cognitive and behavioral dysfunctions in such mice. Here we assessed unconditioned anxiety and conditioned fear responses by challenging Ts65Dn mice in the elevated plus maze (EPM) and Pavlovian fear conditioning tests. Baseline analysis showed that Ts65Dn mice had increased percentage of time spent in the open arms compared to euploid control mice during the test session in the EPM, while there was no difference in the percentage of time spent in the closed arms between those mice. During the context test, control mice displayed a larger percentage of freezing compared to Ts65Dn mice. Our behavioral results confirm previous findings by others of decreased general anxiety and deficits in fear acquisition for Ts65Dn mice. Due to the modulatory role of GABA in synaptic plasticity, we also assessed the effects of GABA on theta burst stimulation (TBS; 5 trains of 4 pulses at 100 Hz, 200 ms intertrain interval) LTP in Ts65Dn and euploid control derived slices. We found that the application of 200 μM GABA decreased TBS LTP at Schaffer collateral-CA1 synapses in hippocampal slices from Ts65Dn when compared to slices from euploid control mice. These experiments, which are still ongoing, should provide us with a better understanding of the role of GABAergic modulation of behavioral and electrophysiological phenotypes in this important mouse model of DS.

Disclosures: D.B. Victorino: None. **J.J. Scott-McKean:** None. **S. Baker:** None. **C.A. Scorza:** None. **A.C.S. Costa:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

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Program #/Poster #: 459.14/A60

Topic: A.07. Developmental Disorders

Support: National Institute of Mental Health grant # R01-MH100144
Swiss National Science Foundation
Ohio State University College of Medicine Endowment
Clinical and Translational Science award 8UL18TR000090-05 from the National Center for Translational Sciences

Title: On the implementation of computational psychiatry to study ADHD subtype differences

Authors: *N. GING-JEHLI[1], E. ARNOLD[1], R. RATCLIFF[1], R. DE BEUS[2], S. CONNOR[2], C. PANCHYSHYN[1], A. LINGEL[1];
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Abstract: Attention-Deficit and Hyperactivity Disorder (ADHD) is a frequent neurodevelopmental disorder, but the neurophysiological and cognitive underpinnings of ADHD remain incompletely explained. For example, neurocognitive test procedures that could be used to differentiate ADHD from controls remain unclear. Similarities and differences between various phenotypes of ADHD are not established thus far. Discriminating between ADHD phenotypes is important, because evidence suggests that different phenotypes respond differently to certain treatments.
The field “Computational Psychiatry” can link specific cognitive components with ADHD phenotypes. Applying the Ratcliff Diffusion Model (RDM) to the performances of children aged 7 to 10 with (N=74) and without (N=60) ADHD on the “Integrated Visual and Auditory Continuous Performance Test” (IVA), we examine cognitive differences among the different ADHD presentations (subtypes) distinguished by the Diagnostic and Statistical Manual of Mental Disorders (DSM), and between the ADHD subtypes and controls.
Applying such a computational approach, we have found strong sequential effects and significant differences between ADHD subtypes. Specifically, when stimuli are auditorily presented, the ADHD predominantly inattentive presentation (ADHD-I) exhibits a greater bias towards repeating previously made choices, as indexed by starting point biases, than the ADHD, combined presentation (ADHD-C) [$F(1,72)=7.106$, $p=0.009$, $\eta p^2=0.090$].
Moreover, a repeated mixed-model ANCOVA, adjusting for gender, suggests: in comparison to ADHD-I, when target stimuli are frequently presented, ADHD-C is better (e.g., faster and more accurately) able to detect visually presented non-target stimuli, as indexed by higher drift rates ($p=0.014$). In contrast, when non-target stimuli are frequently presented, ADHD-C is better able

to detect visually presented target stimuli, as indexed by higher drift rates (p=0.019). Hence, while ADHD-C have higher drift rates for infrequently presented stimuli, ADHD-I have higher drift rates for frequently presented stimuli, but only when they are auditorily presented (p=0.004).
Currently, we are collecting data of children without ADHD (N=60) to examine whether: i) the sequential effects found are a hallmark of ADHD, and ii) the RDM could be used to not only distinguish between ADHD subtypes, but also between children with and without ADHD. Eventually, linking EEG measures to RDM parameters suggests that the RDM may be used to measure a broader spectrum of ADHD phenotypes (e.g., late starters, mind wanderers) that may show deficits in distinct cognitive components.

Disclosures: **N. Ging-Jehli:** None. **E. Arnold:** A. Employment/Salary (full or part-time):; The Ohio State University Wexner Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Curemark, Forest, Lilly, Neuropharm, Novartis, Noven, Shire, Supernus, Roche, YoungLiving, Autism Speaks. F. Consulting Fees (e.g., advisory boards); Gowlings, Neuropharm, Organon, Pfizer, Sigma Tau, Shire, Tris Pharma, Waypoint, Arbor, Ironshore, Novartis, Noven, Otsuka, Pfizer, Roche, Seaside Therapeutics. **R. Ratcliff:** None. **R. de Beus:** None. **S. Connor:** None. **C. Panchyshyn:** None. **A. Lingel:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.15/A61

Topic: A.07. Developmental Disorders

Support: Medical Research Council is funding this project

Title: Increased left inferior fronto-striatal activation during error monitoring after fMRI neurofeedback of right inferior frontal cortex in ADHD

Authors: ***M. CRIAUD**, M. WULFF, A. A. ALEGRIA, G. BARKER, V. GIAMPIETRO, K. RUBIA;
Inst. of Psychiatry, Psychology & Neuroscience; King's Col. London, London, United Kingdom

Abstract: ADHD is associated with poor self-control, underpinned by inferior fronto-striatal deficits including poor self-monitoring skills typically associated with reduced activation in error monitoring networks of left inferior frontal cortex (IFC), insula, cingulate and striato-thalamic regions. We showed previously that 11 runs of 8.5 minutes of real-time functional magnetic resonance imaging neurofeedback (fMRI-NF) of right IFC in 18 ADHD adolescents resulted in

increased activation in rIFC as well as of entire fronto-cingulo-striatal networks,which were associated with clinical symptom improvement. Furthermore, rIFC-NF also increased activation in rIFC and parietal areas during successful Stop task performance. In this study, we investigated whether fMRI-NF would also improve the neural correlates of error monitoring during failed stop trials. Twenty-seven boys with ADHD underwent fMRI-NF; 16 in the active group received fMRI-NF of the rIFC and 11 in the control group received fMRI-NF of the left parahippocampal gyrus. They performed a tracking fMRI Stop task before and after fMRI-NF. An ANOVA time (pre- vs post-fMRI NF) x group (active vs control) was applied to brain activation and performance to failed stop trials. We furthermore tested for correlations between brain changes and performance and clinical changes. The active relative to the control group showed increased activation in left IFC, insula and putamen during the failed stop trials, after relative to before fMRI-NF. This activation change was furthermore correlated with decreased post-error reaction times, indicating more efficient error monitoring, and trend-wise with decreased clinical symptoms. fMRI-NF of rIFC improved performance and activation of left-hemispheric IFC-insular-striatal regions during error monitoring in association with clinical symptom improvement. The findings show that rIFC-NF of rIFC has more widespread upregulation effects - not limited to right IFC- that extend to contralateral fronto-insular-striatal areas of error monitoring, which have previously been shown to be upregulated with stimulant medication.

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Poster

459. Neural Mechanisms for Developmental Disorders I

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Topic: A.07. Developmental Disorders

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Title: Foveal hypoplasia in a genetically engineered anole lizard

Authors: *C. SABIN[1], A. M. RASYS[2], B. M. MCKINNON[3], J. COLCLOUGH[1], H. KIM[4], D. MENKE[1], J. D. LAUDERDALE[2];
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Abstract: In humans, mutations in genes that impact melanin synthesis or melanosome biogenesis and trafficking in cells of the retinal pigmented epithelium (RPE) result in visual

defects. These defects include the loss or abnormal development of the fovea and misrouting of the normal ipsilateral axon projections from the retina to the brain. The link between the pigmentation pathway and retinal development is poorly understood but almost certainly involves signaling between the RPE and non-pigmented neural retina. We hypothesize L-DOPA production by the RPE cells acts to control development of the fovea. Recent studies have established that L-DOPA can act on RPE cells in an autocrine manner through GPR143, a G protein-coupled receptor, to increase secretion of SERPINF1 (also known as PEDF). SERPINF1, a multifunctional secreted glycoprotein and a non-inhibitory member of the serine protease inhibitor (serpin) family, is known to exhibit diverse and significant biological activities including the regulation of neural differentiation. Other studies have suggested that L-DOPA may play a direct role in cell proliferation and/or neurogenesis. Rodents and many other mammals, such as dogs and cats, lack fovea and cannot be used to test if disruptions in L-DOPA production, GPR143 signaling activity, or SERPINF1 release have any effects on fovea development. Therefore, we are developing the brown anole, *Anolis sagrei*, as a model system to study the cellular and molecular mechanisms underlying foveal development. These small lizards of the Caribbean are normally bifoveated, with morphologically distinct fovea in the central and temporal retina. As proof-of-principle, we have used CRISPR-cas9 to generate a series of mutations in the *tyrosinase* gene of *A. sagrei*. Lizards harboring loss-of-function *tyr* mutations exhibit an absence of pigmentation and loss of the temporal retina. These findings suggest the lizard is a useful model to investigate the underlying effects of albinism on fovea formation.

Disclosures: **C. Sabin:** None. **A.M. Rasys:** None. **B.M. McKinnon:** None. **J. Colclough:** None. **H. Kim:** None. **D. Menke:** None. **J.D. Lauderdale:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.17/A63

Topic: A.07. Developmental Disorders

Support: NIH Grant T32GM007103
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NSF Grant #1827647

Title: Elucidating the role of tyrosinase in fovea development using the Anolis sagrei lizard

Authors: ***B. M. MCKINNON**[1], A. M. RASYS[2], D. B. MENKE[1], J. D. LAUDERDALE[2]; [1]Genet., [2]Cell. Biol., Univ. of Georgia, Athens, GA

Abstract: Although most often associated with color diversity in animals, pigments play a critical role in vision by protecting cells from harmful wavelengths of light. Pigment production

is also thought to be important for eye development—particularly with the formation of the fovea. The fovea is a pit/depression found in the retina in a region where there is a high density of photoreceptor cells that are crucial for a person's high visual acuity. When pigmentation is absent, a condition known as albinism, the fovea fails to develop and, in such individuals, vision is often extremely poor. The most commonly mutated gene in albinism is *tyrosinase*, which encodes an enzyme that mediates the conversion of precursors (i.e. L-tyrosine into L-DOPA and L-DOPA into Dopaquinone) necessary for melanin synthesis. Because current model systems to study eye development, like the mouse, chick, and zebrafish, lack a fovea, it is unclear how affecting this pathway leads to a dysregulation of fovea formation. To address this, our lab recently established CRISPR genome editing tools in the *Anolis sagrei* lizard—a novel foveated model system and created the first *tyrosinase* mutant lizard. By using *tyrosinase* mutant lizards and pharmacological agents that affect the melanin synthesis pathway, we aim to determine when tyrosinase activity is crucial for fovea formation in embryonic development. Towards this goal, we have developed an egg drug-delivery system and describe here the histological effects of 1-phenyl-2-thiourea, a drug known to inhibit tyrosinase, in the developing wild-type lizard embryonic eye. This work lays the foundation for understanding how pathways governing pigment production may regulate fovea development in *Anolis* lizards.

Disclosures: B.M. McKinnon: None. **A.M. Rasys:** None. **D.B. Menke:** None. **J.D. Lauderdale:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.18/A64

Topic: A.07. Developmental Disorders

Title: Lactational ethanol exposure: Brain and behavioral development in a breastfeeding model

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Abstract: Prenatal ethanol exposure (PrEE) alters neocortical connectivity, gene expression, and behavior in offspring. Early postnatal exposure in humans, from ethanol in breastmilk, can result in low body mass, and verbal IQ scores, as well as altered infant sleeping patterns. In the US, approximately 36% of breastfeeding mothers consume alcohol; incidence rates are higher in Australia (60%) and, surprisingly, lower in Canada (20%) (Popova et al., 2013; Tay et al., 2015; May et al., 2016). Here, we investigate how lactational ethanol exposure (LEE) impacts brain and behavioral development using a novel CD-1 breastfeeding mouse model. Control dams were provided water throughout gestation and all dams were given unlimited chow. Dams in the experimental group were given a 25% EtOH in water solution *ad libitum* when pups were 6 days

old (postnatal day (P) 6) until weaning at P20. P6 was chosen for the start of LEE as P7 in mice is approximately equivalent to the day of birth in humans. At weaning, a subset of LEE and control mice were euthanized for P20 experiments while the remaining offspring were separated from the dam and raised without ethanol until P30, when behavioral assays were performed. Dam blood ethanol content (BEC) and plasma osmolality (POSM, a measure of hydration) were measured at weaning. Experimental dams had significantly higher BECs when compared to controls, as did LEE pups at P20, as expected. POSM did not differ between experimental and control dams or LEE and control offspring at P20. LEE mice had decreased body and brain weights at P20 when compared to controls. However, these phenotypes were rescued by P30. *In situ* RNA hybridization was used to examine neocortical expression of two genes important for patterning in brain development, *Id2* and *RZRβ*. Laminar and region-specific expression patterns within neocortex were observed in LEE and control offspring at P20 and P30. A series of behavioral assays were conducted in all offspring at P30. LEE mice spent significantly more time in the open arms of the Elevated Plus Maze, suggesting increased risk-taking behavior, as has been observed previously in PrEE mice from our laboratory. There were no significant differences observed between LEE and control mice at age P30 on the Forced Swim Test (depressive behavior), the Suok Assay (sensorimotor integration) or the 3-chamber Sociability Test (social behavior). There is a paucity of research regarding the dangers of maternal consumption of alcohol during breastfeeding and studies such as this, using animal models of lactational exposure, are important to advance our understanding and recommendations of safe maternal practices in early infancy.

Disclosures: R.F. Perez: None. **K.E. Conner:** None. **M. Nabatanzi:** None. **K.J. Huffman:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.19/A65

Topic: A.07. Developmental Disorders

Title: Embryonic gross anatomy in mouse model of FASD

Authors: *K. E. CONNER[1], K. J. HUFFMAN[2];
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Abstract: Fetal alcohol spectrum disorders (FASD) describe a wide array of phenotypes that arise in offspring whose mothers consumed alcohol, or ethanol, during pregnancy (Hoyme et al., 2016). It is currently estimated that 5% of children born in the United States have been affected by maternal consumption of alcohol during pregnancy; this number may be underestimated due

to lack of reporting (May, et al., 2018). Previous work in our laboratory has documented many deleterious effects of prenatal ethanol exposure (PrEE) via multilevel experiments in a novel CD-1 mouse model of FASD. For example, abnormal neocortical gene expression, altered neuroanatomy, and development of ectopic intraneocortical connections in postnatal mice were induced by PrEE (El Shawa et al., 2013; Abbott et al., 2016). Many of these phenotypes were passed to subsequent generations, as demonstrated in our transgenerational model of FASD (Abbott et al., 2018). In our prior work, we focused on the postnatal effects of PrEE. In the current study, we extended our research by investigating the effects of PrEE in embryonic mice. We have identified gross neuroanatomical phenotypes in PrEE and control offspring at different embryonic stages prior to birth (embryonic day (E) 12.5, E14.5, E16.5, E18.5) in our mouse model of FASD. *Methods:* Adult dams self-administered 25% EtOH *ad libitum* beginning immediately after confirmation of conception via detection of the vaginal plug. At the preselected embryonic dates, dams were cervically dislocated and a postmortem caesarian section was performed to extract embryos. Embryos were euthanized via hypothermia. The E12.5 and E14.5 embryos were exsanguinated post mortem; the E16.5 and E18.5 embryos were transcardially perfused with 4% PFA (pH=7.4). All embryos were then post-fixed in PFA and examined for gross physical and neuroanatomical differences. *Results*: PrEE embryos were smaller than controls at all ages; they also consistently exhibited decreased body weights. Additionally, brain weights were significantly lower in PrEE embryos compared to controls at all ages. Cortical lengths were significantly reduced in PrEE embryos at E14.5, E16.5, and E18.5 when compared to controls. Variations in facial morphology were observed between control and experimental groups. By examining anatomical defects present before birth in our mouse model of FASD, we can gain additional insight into the mechanisms that may regulate the atypical developmental features we have described postnatally in these mice. Elucidating the developmental trajectories of prenatal ethanol exposure-related deficits will aid in our understanding and prevention of FASD in humans.

Disclosures: K.E. Conner: None. **K.J. Huffman:** None.

Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.20/A66

Topic: A.07. Developmental Disorders

Title: Multi-unit electrophysiological mapping of neocortex and behavior in a mouse model of FASD

Authors: *R. T. BOTTOM[1], K. E. CONNER[1], M. ENGLUND[3], C. R. PINEDA[3], C. S. BRESEE[3], M. NABATANZI[2], L. A. KRUBITZER[3], K. HUFFMAN[2];

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Abstract: Fetal alcohol spectrum disorders (FASD) describe the range of adverse neurological and behavioral effects that result from prenatal ethanol exposure (PrEE). Human behavioral and imaging data suggest that the neocortex constitutes a focal point of ethanol's teratogenic effects. Accordingly, rodent models of FASD have described widespread neocortical dysfunction including altered cortical cell migration and postsynaptic current frequencies *in vitro* (Delatour et al., 2018), as well as aberrant patterns of neuronal connectivity and gene expression (Abbott et al., 2018). This suggests an overall disorganized neocortex due to PrEE. However, no study has directly examined the impact of PrEE on the functional organization of sensory areas within neocortex and related it to behavioral phenotypes. To address this, we conducted behavioral assays and multiunit electrophysiological recordings in 6-month-old PrEE mice using our previously established prenatal exposure model, created with 25% ethanol dam self-administration (El Shawa et al., 2013). Prior to electrophysiological experiments, we assessed behavior using a battery of assays. Adult PrEE mice spent significantly more time in open arms of the elevated plus maze as compared to controls, suggesting increased risk-taking behavior. Also, PrEE mice showed impairment on the Accelerated Rotarod and social behavior as measured on the 3- chambered social approach test. No differences were observed between groups on the forced swim assay. After completion of behavior tests, PrEE and control mice underwent electrophysiological experiments. Multiunit neuronal activity was recorded at a number of closely spaced sites across the neocortex and the type of sensory stimuli that elicited a response, as well as the receptive field for neurons at all somatosensory sites, was recorded. Stimuli used to elicit responses included visual (light flash), auditory (clicks), and somatosensory (tactile). Analyzing electrophysiological recording data matched to cytochrome oxidase stained tissue, we were able to create maps of sensory neocortex in both PrEE and control mice and observed boundaries between specific sensory regions. It is clear that PrEE induces long-term behavioral effects in the offspring, spanning to later adulthood, in a mouse model of FASD. Additionally, this is the first study where functional, electrophysiological maps of the adult PrEE neocortex have been established and results of this study will provide key information regarding how functional features of the adult neocortex relate to behavioral phenotypes in FASD.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.21/A67

Topic: A.07. Developmental Disorders

Title: Type 3 metabotropic glutamate receptor (mGluR3) modulates postnatal microglia reactivity in a rat model of fetal growth restriction

Authors: M. ZINNI[1], J. PANSIOT[1], F. FAZIO[2], L. IACOVELLI[3], R. ORLANDO[3], D. VAIMAN[4], F. NICOLETTI[2], O. BAUD[1,5,6], *J. MAIRESSE[6,1];
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Abstract: Fetal growth restriction (FGR) is a neurodevelopmental condition associated with high risk to develop cognitive and neurobehavioral handicaps. Abnormal neuro-inflammatory responses orchestrated by microglia cells lies at the core of this abnormal neurodevelopmental trajectory. Thus, normalization of microglia reactivity could represent a promising therapeutic strategy. During the perinatal period the neurotransmitter glutamate plays both positives and negatives roles depending on the receptors and cells types on which its action is considered. Metabotropic glutamate receptor (mGluR3) activation reduce neuro-inflammation in several adult pathological conditions (e.g Alzheimer, schizophrenia). However, mGlu3 receptors function is totally unexplored on microglia in the context of neurodevelopmental disorders and in the early postnatal period when his expression is high.
We developed a rat model of FGR (gestational low-protein diet + IL-1b, i.p. at postnatal days (PND) 1 & 2, LPD IL-1b) that shows increased early pro-inflammatory microglia reactivity conducing to cognitive and behavioral disorders. Magnetic sorted microglia from PND4 CTRL and LPD IL-1b pups are analyzed by Affymetrix assay. The expression of GRM3 is analyzed in CTRL and LPD IL-1b cortex and microglia cells at PND1, 2, 4 & 7, and protein level is analyzed at PND4 & 7. PND4 & 7-cultured microglia are treated with the mGluR3 agonist (LY 379268) prior to a pro-inflammatory challenge with IL-1b and INFg for the measurement of pro- and anti-inflammatory markers and of GRM3. Same experiments are performed in presence of the mGluR3 negative allosteric modulator, LY 2389575, only in CTRL cells.
Microglia microarray analysis evidenced that GRM3 is the highly expressed GRM at PND4 and the most down-regulated by LPD IL-1b. This result is confirmed by RT-qPCR from PND2 to 7 and by western blot at PND4 & 7. Low levels of GRM3 are observed in LPD IL-1b cortex at PND2 & 4. Reduced GRM3 expression is confirmed on PND4 & 7 microglia cultures from LPD IL-1b and is associated to pro-inflammatory phenotype both in basal and IL-1b+INFg conditions. Expression of pro-inflammatory markers is reduced in presence of mGluR3 agonist in both groups. The ability of mGluR3 to modulate inflammatory response is confirmed by the increase of pro-inflammatory cytokines observed in response to LY 2389575.
In conclusion, reduced postnatal mGluR3 microglia expression/stimulation is associated to increased pro-inflammatory cell activity and reactivity. The modulation of central inflammatory response by mGluR3 activation could then represent a valid therapeutic strategy to improve the neuro-protection in the immature brain.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.22/A68

Topic: A.07. Developmental Disorders

Title: Structural and functional brain imaging in a rat model of fetal growth restriction

Authors: J. MAIRESSE[1,2], *Y. VAN DE LOOIJ[1,3], C. DEMENÉ[4], J. PANSIOT[2], M. ZINNI[2], S. V. SIZONENKO[1], M. TANTER[4], O. BAUD[1,5,2];
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Abstract: Fetal Growth Restriction (FGR) is one of the most common deleterious antenatal conditions in newborns, leading to a significant increase in perinatal mortality, neurological handicaps and chronic diseases in adulthood. Interestingly, the brain injuries and the subsequent neurodevelopmental impairments observed in children born growth restricted seem to be closely associated with an exacerbated neonatal neuro-inflammation. In this context, advance in early life neuroimaging in animal model of FGR associated with neuro-inflammation represents major opportunity for diagnosis, prognosis and targeted therapeutic strategies. We developed a rat model of FGR (gestational low-protein diet + IL-1b, i.p. at postnatal days (P) 1 & 2, LPD/IL-1b) that shows increased pro-inflammatory microglia reactivity at P2 & P4 leading to a reduced myelination at P10 and cognitive and behavioral disorders in young adults animals. Here, we investigated structural and functional abnormalities associated with FGR and postnatal neuro-inflammation in this model. At P10 and P21, advanced ex-vivo diffusion MRI techniques, DTI (diffusion tensor imaging) and NODDI (neurite orientation dispersion and density imaging), performed at 9.4T were used to investigate brain cortical and white matter microstructure. Axial and radial diffusivities and fractional anisotropy were found significantly reduced in LPD/IL-1b animals in most of the observed structures (cingular cortex and white matter, somatosensory cortex dorsal, corpus callosum and external capsule). Conversely, intra-neurite volume fraction and orientation dispersion index were found significantly increased. At P26/28, we used high-resolution functional UltraSound (fUS) to generate highly sensitive cerebral blood volume (CBV) maps underlying neuronal activity in order to assess inter- and intra- hemispheric cortical

functional connectivity. fUS imaging revealed that FGR was associated with a significant reduction in intra- and inter-hemispheric connectivity in most of the explored cortical area. In conclusion, our rat model of FGR associated to early postnatal neuro-inflammation recapitulated microstructural and functional cortical alteration readily observable by advanced neuroimaging technics. Innovative neuroimaging tools used in this study pave the way for their translational use in human neonates and to assess new neuroprotective therapies.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.23/A69

Topic: A.07. Developmental Disorders

Title: Distribution of neurofilament immunoreactive neurons (SMI-32) in the prefrontal cortex in Williams syndrome

Authors: *B. HRVOJ MIHIC[1], K. L. HANSON[2], C. H. LEW[3], D. N. CUEVAS[3], D. GREINER[3], K. SEMENDEFERI[4];
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Abstract: Williams syndrome (WS) is a neurodevelopmental disorder characterized by a set of compromised features in social behavior, including an increased desire to interact socially with strangers and inadequate responses to social situations. Several regions of the prefrontal cortex involved with processing of socially salient information - including the frontal pole and the orbitofrontal cortex -- display abnormalities in WS: decreased density of neurons compared to controls, and deficiencies in length and branching of dendrites, and the number of dendritic spines in the prefrontal cortex compared to unimodal cortical areas. Supragranular (layers II/III) are more affected than infragranular layers (layers V/VI). In order to examine if a particular subclass of neurons within the prefrontal cortex is affected in WS, we used an antibody against non-phosphorylated epitope of neurofilament protein (SMI-32) to examine distribution of SMI-32ir neurons in the frontal pole of WS and neurotypical controls. SMI-32ir neurons represent important parts of cortical circuitry, underlying long cortico-cortical connections. They are especially prominent in supragranular layers in the prefrontal cortex and have previously been implicated in deficiencies in schizophrenia, bipolar disorder, and other psychiatric disorders. Our analysis revealed that SMI-32ir neurons in WS occupied the same relative position within layer III as in neurotypical controls, being restricted to the lower layer III of the frontal pole, but with important differences between WS and controls. More specifically, we found that density of

SMI-32ir neurons was lower in WS and the neurons were characterized by smaller cell bodies. These findings imply that lower layer III magnopyramidal neurons in the prefrontal cortex appear particularly affected in WS, suggesting deficiencies in cortico-cortical connectivity between the frontal pole and other cortical regions in the disorder.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.24/A70

Topic: A.07. Developmental Disorders

Support: NIH Grant MH113352
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Roy J. Carver Charitable Trust

Title: Mutations of E3 ubiquitin ligase adaptor protein KLHL15 in X-linked intellectual disability

Authors: *J. SONG[1], R. MERRILL[1], R. KEPHART[1], Y. LIU[1], M. SHAW[2], R. CARROLL[2], A. GARDNER[2], L. JOLLY[2], F. MCKENZIE[3], J. GECZ[2,4], V. KALSCHEUER[5], S. STRACK[1]; [1]Dept. of Pharmacol., Univ. of Iowa, Iowa City, IA; [2]Adelaide Med. Sch. and Robinson Res. Institute, The Univ. of Adelaide, Adelaide, Australia; [3]Genet. Services of Western Australia, Women and Newborn Hlth. Service, King Edward Mem. Hosp., Subiaco, Australia; [4]South Australian Hlth. and Med. Res. Inst., Adelaide, Australia; [5]Max Planck Inst. for Mol. Genet., Department of Human Molecular Genetics, Germany

Abstract: Intellectual disability (ID), which affects 1-2% of the general population, is a devastating neurodevelopmental disorder with the most lifetime costs of all diagnoses in the U.S. However, males are more susceptible to ID than females and are often found to have severe outcomes. Mutations in Xchromosomal genes are thought to account for this male-biased phenomenon. KLHL15 was recently identified as a novel XLID gene. It encodes Kelch-like protein 15 (KLHL15), a substrate adaptor of a Cullin-3 (CUL3)-based E3 ubiquitin ligase complex that targets proteins, including the brain-enriched B′β regulatory subunit of protein phosphatase 2A (PP2A), for degradation by the ubiquitin/proteasome system (UPS). Several KLHL15 mutations have been found in the poorly characterized BACK domain, which is a "hotspot" for many deleterious variants of the other KLHL family members resulting in either Mendelian diseases or human cancers. We identified both loss-of-function (ΔFY241, ::ACOT9)

and gain-of-function (R249H) alleles, and we hypothesize that small deletions and point mutations in KLHL15's BACK domain lead to structural rearrangement that change the alignment between bound substrates and the ubiquitin transfer (E2/E1) complex to either slow or accelerate substrate ubiquitination and degradation, causing dysregulated protein turnover of CUL3KLHL15-targeted substrate(s) and eventually pathogenesis of ID.In addition, we applied bioinformatic approach coupled with mass spectrometry to identify other brain- and neuron-specific substrates also targeted by KLHL15 for polyubiquitination and proteaosomal degradation, which may uncover other molecular mechanisms underlying XLID and neurodevelopmental disorders (NDDs) in general.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.25/A71

Topic: A.07. Developmental Disorders

Title: Characterization of a novel rat model of creatine transporter deficiency

Authors: *M. WRIGHT, K. POKSAY, A. TROTIER-FAURION, B. CASS, S. BROWN, K. JAYASHANKAR, M. ANDREWS, S. FYFFE-MARICICH;
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Abstract: Creatine transporter deficiency (CTD) is a rare X-linked inherited disorder, caused by loss of function mutations in the *SLC6A8* gene which encodes the creatine transporter (CrT). CrT protein expression at the blood-brain barrier and in neurons helps supplement intraneuronal creatine pools in the brain as a source of ATP-energy. Without functional CrT, creatine pools become depleted, thus impairing the normal metabolic function in these cells. Patients with CTD experience global developmental delay, intellectual disability, autistic features, behavioral disorder, and delayed language development. There are no currently approved treatments for CTD.
Here we describe a rat model of CTD generated by deleting exons 2-4 from *SLC6A8* using CRISPR/Cas9 technology. The larger brain size of rats relative to mice allowed us to isolate intact neurons and analyze the intracellular creatine levels from individual $SLC6A8^{+/Y}$ (WT) and $SLC6A8^{-/Y}$ (CTD) rats. Brain histology, endogenous whole brain creatine levels, and a battery of behavioral phenotypes were also assessed. The brains of CTD rats showed no overt structural changes, consistent with previously published mouse models of CTD as well as patients with CTD. Endogenous creatine levels in both a whole brain homogenate, and in neuronally-enriched

cell isolates, were decreased by greater than 80% compared to WT. Additionally, whole brain homogenates from CTD rats dosed with d3-labeled creatine showed that exogenously delivered creatine was not quantifiable in brain tissue. Consistent with patients, *in vivo* ^{1}H- and ^{31}P-MRS analysis also demonstrated significantly decreased levels of endogenous brain creatine in the CTD rat brain (see poster by Lehtimäki and Fyffe-Maricich). The body weights of CTD rats were significantly lower than WT littermates possibly due in part to dental malocclusions that may have impacted food consumption. Behaviorally, CTD rats did not present with a strong behavioral phenotype compared to WT animals across a battery of motor and cognitive tests. This lack of a robust behavioral phenotype in the CTD rats is in contrast to what has been reported in mouse models of CTD, suggesting potential species-specific differences.
In summary, these data support the use of this CRISPR CrT KO rat as a model of CTD for evaluation of pre-clinical therapeutic candidates whose mechanism of action is defined by their ability to restore neuronal creatine concentrations.

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Poster

459. Neural Mechanisms for Developmental Disorders I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 459.26/A72

Topic: A.07. Developmental Disorders

Title: Longitudinal magnetic resonance spectroscopic (^{1}H and ^{31}P MRS) characterization of total and phosphorylated brain creatine in a novel creatine transporter deficient rat

Authors: *K. LEHTIMÄKI[1], B. SULLIVAN[2], K. JAYASHANKAR[2], M. ANDREWS[2], A. J. NURMI[1], S. FYFFE-MARICICH[2];
[1]Charles River Discovery, Kuopio, Finland; [2]Ultragenyx Pharmaceut. Inc., Novato, CA

Abstract: Creatine transporter deficiency (CTD) is a rare X-linked inherited disorder, caused by loss of function mutations in the SLC6A8 gene which encodes the Creatine transporter. Loss of the Creatine transporter leads to low levels of creatine, resulting in a spectrum of disease manifestations including intellectual disability, delayed/absent speech and behavioral disabilities (Clark and Cecil, 2015, Pediatric Res). There are currently no approved treatments for this condition.
A novel SLC6A8 knock-out CTD rat model was generated, utilizing CRISPR/Cas9 technology, to evaluate pre-clinical therapeutic candidates (see poster by Wright and Fyffe-Maricich for full characterization details). The purpose of this study was to measure the longitudinal variability of Creatine (Cr) and Phosphocreatine (PCr) levels in the brain of live CTD rats by ^{1}H and ^{31}P-Magnetic Resonance Spectroscopy (MRS).

MRS experiments were performed using a 11.7T small animal system (Bruker BioSpin, Ettlingen, Germany), with high gradient strength and shims up to 4th order allowing high spectral resolution and narrow linewidths to distinguish the closely resonating PCr and Cr. ^{1}H MRS was acquired from a hippocampal voxel, while the ^{31}P MRS was acquired from a large forebrain voxel in order to increase the signal-to-noise ratio. MRS experiments were performed at three time points, each separated by 2 weeks. This study employed age-matched CTD rats of following genotypes: wildtype (WT) littermate male n=5, heterozygote (HET) female n=5 and hemizygote (HEMI) male n=5.
Repeat MRS measurements with multiple isoflurane anesthesia events were well tolerated by CTD rats of all genotypes. Both ^{1}H- and ^{31}P-MRS experiments demonstrated a gene-dose-dependent decrease of Cr and PCr (WT>HET>HEMI). The Cr levels measured by ^{1}H-MRS were significantly different between each group (WT = 8.64 +/- 0.51 mmol/kg, HET = 5.44 +/- 0.54 mmol/kg and HEMI = 1.71 +/- 0.13 mmol/kg; mean +/- stdev). ^{31}P-MRS demonstrated significantly lower PCr levels in the CTD rats compared to wild type (WT = 3.78 +/- 0.9 a.u., HET = 2.56 +/- 0.8 a.u. and HEMI = 0.66 +/- 0.1 a.u.; mean +/-stdev). The biologic variability over the three visits was <13.14%CV for Cr (measured by ^{1}H-MRS) and <41.67%CV for PCr (measured by^{31}P-MRS).
In summary, low levels of brain Cr and PCr measured by MRS in a novel rat model recapitulates observations from patients with CTD. This model has an adequate dynamic range and stability to be appropriate for future translational studies.

Disclosures: K. Lehtimäki: None. **B. Sullivan:** None. **K. Jayashankar:** None. **M. Andrews:** None. **A.J. Nurmi:** None. **S. Fyffe-Maricich:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.01/A73

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

Support: ARC grant DP180100636

Title: Behavioural signatures of a developing neural code

Authors: *L. AVITAN, Z. PUJIC, J. MÖLTER, M. MCCULLOUGH, S. ZHU, B. SUN, A. MYHRE, G. J. GOODHILL;
The Univ. of Queensland, Queensland Brain Inst., Brisbane, Australia

Abstract: During early life, the neural code must develop to appropriately transform sensory inputs into behavioural outputs. However little is known about how developments in neural representations directly impact behaviour. To address this we used 2-photon calcium imaging of

GCaMP6s zebrafish larvae and and high speed recording of prey-capture behaviour at different ages. We showed behaviourally a spatial shift in prey detection in the visual field during early life, which is mirrored by a developmental shift in the locus of neural activity in the optic tectum. Decoding of spatial position from tectal activity improved with age at different rates across the tectum, and could predict individual differences in prey-capture behaviour. The dimensionality of evoked activity was higher than that of spontaneous activity, and some statistics of evoked activity became more distinct from those of spontaneous activity with age. Together these results show that developmental signatures of an emerging neural code can be directly related to observable properties of behaviour.

Disclosures: **L. Avitan:** None. **Z. Pujic:** None. **J. Mölter:** None. **M. McCullough:** None. **S. Zhu:** None. **B. Sun:** None. **A. Myhre:** None. **G.J. Goodhill:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.02/A74

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

Support: CRSNS ANR

Title: Gene network control of cortical neuronal circuit assembly

Authors: *S. ZEPPILLI[1,2], A. BOYREAU[2], A. FLEISCHMANN[1], A. CROMBACH[3]; [1]Neurosci., Brown Univ., Providence, RI; [2]Col. de France, Paris, France; [3]Inria, Lyon, France

Abstract: A defining characteristic of the mammalian cortex is its enormous diversity of cell types. Earlier studies have provided insight into the genetic control of cell type specification in the neocortex (NCx). In contrast, the genetic mechanisms underlying the development of the olfactory cortex (piriform cortex, PCx), an evolutionarily old allocortical structure, remain poorly understood. Our lab has recently identified molecular signatures of PCx connectivity and discovered unexpected similarities and differences in the gene expression patterns in adult mouse NCx and PCx (Diodato et al., 2016). We here present recent results using single nuclei RNA sequencing that refine the molecular characterization of adult mouse piriform neuronal cell types. Based on these results we propose that NCx and PCx development is controlled by overlapping sets of transcription factors. To test this hypothesis we examine the expression of key transcription factors involved in neuronal lineage specification during development, employing immunohistochemistry in cleared brain preparations and light sheet microscopy. Furthermore, we use a computational approach to probe the mechanisms of interaction between the different transcriptional regulators. Genes and their interactions are encoded in a mathematical model of a gene network, and the regulatory structure of the network is inferred by

fitting to expression data obtained from whole-brain imaging experiments. Together, modeling and experiments will reveal the molecular mechanisms of PCx development, uncover key regulatory decision points of cortical neuronal lineage specification and identify similarities and differences between the gene network architecture of NCx and PCx.

Disclosures: S. Zeppilli: None. **A. Boyreau:** None. **A. Fleischmann:** None. **A. Crombach:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

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Program #/Poster #: 460.03/A75

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

Support: Shanghai Municipal Science and Technology Major Project
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National Natural Science Foundation of China Grant 31471042

Title: Characterization of novel starburst amacrine subtypes in zebrafish

Authors: *Y. LI[1,2], A. LEE[1], X. JIA[1], X. TANG[1], X. QIU[1], J. HE[1,2];
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Abstract: In mammal, starburst amacrine cells (SACs) have been reported to have two important functions. While their involvement of the generation of retinal waves that are critical, for the formation of visual circuits in the developing retina, SACs also provide the directional inhibition to retinal ganglion cells to generate centrifugal direction selectivity in the developed retina. Here we are exploring SAC subtypes in zebrafish (Danio rerio). Using single cell RNA sequencing and genetic labeling, we identified two subtypes of SACs, each of which exhibited on- and off-types, characteristic morphology, as well as expressing a specific set of transcription factors. CRISPR/CAS9 knockout assay revealed the genetic knockout of subtype-specific transcription factors led to the loss of both SAC subtypes, which further resulted in the disruption of the optical kinetic reflex in zebrafish.

Disclosures: Y. Li: None. **A. Lee:** None. **X. Jia:** None. **X. Tang:** None. **X. Qiu:** None. **J. He:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.04/A76

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

Support: The Graduate School, Northwestern

Title: Deletion of melanopsin modulates the whole retina transcriptome during postnatal development

Authors: *J. A. LUCAS, S. FELDSTEIN, T. M. SCHMIDT;
Neurobio., Northwestern Univ., Evanston, IL

Abstract: Melanopsin-expressing, intrinsically photosensitive retinal ganglion cells (ipRGCs) respond directly to light and have been shown to mediate a broad variety of visual behaviors in adult animals. In addition to this, ipRGCs have been shown to be the first light sensitive cells in the developing retina, and have been implicated in a number of retinal developmental processes such as pruning of retinal vasculature and refinement of retinofugal projections. However, little is currently known about how melanopsin and ipRGCs drive such broad influences on retinal development or whether they modulate additional, unidentified aspects of retinal development. In order to more broadly understand the influence of ipRGCs on retinal development, we performed RNAseq to compare the retinal transcriptome of wildtype and melanopsin knockout mice at postnatal day (P) 8 and P14. We identified 66 and 374 differentially expressed genes at P8 and P14, respectively. We then cross-validated a subset of significantly differentially expressed genes with qPCR for both age groups, and identified multiple genes that were continued to be differentially expressed in adult retinas. Overall, our work shows that melanopsin expression alters the whole retinal transcriptome during development, and that some of these changes persist into adulthood. This work provides important insight to the diverse molecular impacts of melanopsin on the developing retina, and gene targets for further exploration in their role in retinal development.

Disclosures: J.A. Lucas: None. **S. Feldstein:** None. **T.M. Schmidt:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.05/DP01/A77

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: A.08. Development of Motor/ Sensory/ and Limbic Systems

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Title: Origin and function of directionality in spontaneous retinal waves

Authors: *X. GE, A. GRIBIZIS, M. CRAIR;
Yale Univ., New Haven, CT

Abstract: Before the onset of visual experience, spontaneous retinal waves are the main source of activity in the developing superior colliculus (SC), thalamus and primary visual cortex in the mammalian visual system. Genetic and pharmacological manipulations of this spontaneous retinal activity suggest a causal link between retinal waves and circuit refinement. Previous studies found that Stage II (around the first week after birth in mice) spontaneous waves exhibit a strong directional bias. However, it remains unclear how this bias emerges, whether it changes over development and whether this spatiotemporal feature of spontaneous waves is critical for circuit refinement and the development of functional circuit properties. Here, we describe experiments that investigate the role and origin of spontaneous wave directionality during visual system development.
We used wide-field Ca^{2+} imaging of retinal ganglion cell (RGC) projections in the SC *in vivo* and optogenetic or light stimulation of the retina to examine spontaneous and stimulus induced wave direction bias. We observe that the directional bias emerges at the end of Stage II (~P8) waves and vanishes before the time of eye opening (~P12). The biased direction (temporal to nasal) is consistent between P8 and P12. Notably, the directional bias of wave propagation is not uniform across the retina, but rather resembles the pattern of optic flow in the retina generated by the animal's forward motion. To understand the origin of wave directional bias *in vivo*, we used selective optogenetic stimulation of starburst amacrine cells (SACs), or light stimulation after the onset of light response (~P10), to initiate waves at various locations in the retina. Our experiments suggest that starting from around P10, stimulated retinal waves propagate in a direction consistent with intrinsic waves, regardless of their nucleating sites. This suggests a

biased retinal circuit that favors the propagation of waves in a specific direction on the retina. In addition, we show that pharmacological blockade of inhibition *in vivo*, specifically $GABA_A$ mediated inhibition, diminishes wave directional bias. This result suggests that $GABA_A$ mediated inhibition plays an especially important role in establishing the strong directional bias of spontaneous retinal waves.
In summary, our results suggest a specific developmental stage in which spontaneous retinal waves exhibit a strong directional bias, and that this bias is a result of intrinsic asymmetry in the retinal circuit. This bias could potentially affect visual circuit refinement in the retina and other parts of the visual system during development.

Disclosures: X. Ge: None. **A. Gribizis:** None. **M. Crair:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.06/A78

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

Support: MOST 106-2311-B-002-007

Title: Cholinergic retinal waves are regulated by the dysbindin expression levels in developing retinal ganglion cells

Authors: *T.-L. CHENG[1], M.-H. LU[2], C.-T. WANG[1,3,4,5];
[1]Inst. of Mol. and Cell. Biol., [2]Sch. of Med., [3]Dept. of Life Sci., [4]Neurobio. and Cognitive Sci. Ctr., Natl. Taiwan Univ., Taipei, Taiwan; [5]Genome and Systems Biol. Program, Natl. Taiwan Univ. and Academia Sinica, Taipei, Taiwan

Abstract: Schizophrenia (SCZ) is an idiopathic disease with neurodevelopmental defects. One of the major SCZ susceptibility genes is Dystrobrevin-binding protein-1 (Dysbindin). Previous studies suggested that primary sensory processing, including visual processing, is often impaired in SCZ patients. However, the mechanism of Dysbindin in regulating visual system development remains unknown. During the first postnatal week in rodent, developing retinal neurons display retinal waves, which are essential for the refinement of retinogeniculate synapses. These retinal waves (also termed cholinergic waves) are initiated by starburst amacrine cells (SACs) spontaneously releasing acetylcholine (ACh) and γ-aminobutyric acid (GABA) to neighboring SACs and retinal ganglion cells (RGCs). Our preliminary results suggested that Dysbindin is important for regulating the spatiotemporal properties of cholinergic waves by using non-specific cell-type molecular perturbation. In this study, we aim to delineate the cellular mechanism underlying Dysbindin regulation of cholinergic waves. First, we used immunofluorescence staining to examine the localization of Dysbindin in developing rat retinas (P1-P15) and found

that Dysbindin is highly expressed in synapse layers, such as the inner plexiform layer. Next, we used the cell-type specific promoter (the Brn3b promoter for RGCs) to specifically overexpress or deplete Dysbindin in RGCs. By using live calcium imaging, we further analyzed the wave properties following molecular perturbation. We found that altering the levels of Dysbindin in RGCs specifically changed the interval of cholinergic waves. Therefore, Dysbindin regulation of cholinergic waves may be via RGCs. These results imply that Dysbindin may involve in SCZ pathogenesis through regulating the development of visual circuits.

Disclosures: **T. Cheng:** None. **M. Lu:** None. **C. Wang:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.07/A79

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

Support: ROIEY015788
P30EY025586
U01 NS094358
R01 MH111424

Title: Neonatal neuronal activity of mouse visual structures in the absence of retinal drive

Authors: *M. S. BERNARDEZ SARRIA[1], N. D. FITZGERALD[2], M. C. CRAIR[2];
[1]Interdepartmental Neurosci. Program, [2]Neurosci., Yale Univ., New Haven, CT

Abstract: Early in the development of the mammalian visual system, retinal ganglion cells fire in a coordinated, synchronous spatiotemporal pattern. This activity spreads through the retina as retinal waves, and propagates along the ascending visual pathway to the thalamus (dLGN), superior colliculus (SC) and visual cortex (V1). A leading hypothesis in the field is that this spontaneous activity is key for the proper establishment of visual circuits. The developmental consequences of removing spontaneous retinal drive on central visual structures remains a topic of intense study, and how this activity affects the functional and anatomical development of the cortex in particular, is still poorly understood. Here, we use perinatal denervation (P0-1 enucleation) or neonatal inactivation (intraocular epibatidine) to assess chronic and acute effects of removing retinal input to visual circuit development. Our in-vivo widefield calcium imaging experiments reveal that cortical activity is robust in early postnatal life (P4). Neither acute nor chronic removal of retinal drive abolish activity in primary visual cortex (V1), but do change its properties dramatically. These results suggest that in the absence of retinal innervation or input, central visual structures use existing circuitry to drive activity in V1. Our studies also show that spatial properties of activity and correlations across visual structures are particularly affected by

these manipulations. The effects of denervation (chronic) and inactivation (acute) share important similarities, but they also show key differences that are likely driven by the effects of longer-term (days) homeostatic mechanisms. Generally, developmental neuroscience holds a retina-centric view with respect to activity-mediated assembly of visual circuits. Our results suggest the presence of important, non-peripheral inputs that may contribute to the development of the visual system, and in particular, V1.

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Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.08/A80

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

Support: Ministry of Spain grant 2017/00499/001

Title: *In vivo* wide-field imaging of spontaneous and evoked activity in the developing mouse neocortex

Authors: *T. GUILLAMON-VIVANCOS[1], F. J. MARTINI[2], M. VALDEOLMILLOS[2], G. LOPEZ-BENDITO[3];
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Abstract: Rhythmic patterns of spontaneous activity are essential for the proper formation and maturation of sensory systems and have been described in several structures of the developing brain, including the retina or the thalamus. Previous work from our lab has demonstrated that waves of spontaneous activity in the embryonic thalamus are involved in the formation of cortical sensory maps. In the cortex, most studies of synchronized activity have been done *in vitro* or at postnatal stages when cortical maps are already formed. Here, we used *in vivo* wide-field imaging of calcium transients to identify patterns of activity in the embryonic and early postnatal cortex of the mouse. Using a stimulation paradigm of the whisker pad we were able to correlate the topography of the emerging somatosensory map with the spontaneous activity that occurs at these stages. In early sensory deprivation models, we found that the pattern of calcium activity that prefigures the formation of maps is altered already in the embryo, which unveils that cross-modal plasticity changes occur earlier than previously thought.

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Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.09/A81

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

Support: NIH Grant EY019924-08
Knights Templar Eye Foundation
Research to Prevent Blindness /Lions Club International Foundation

Title: Static and dynamic visual search in cerebral visual impairment using virtual reality and multi-modal neuroimaging paradigm

Authors: *C. R. BENNETT[1], E. S. BAILIN[2], C. M. BAUER[3], P. J. BEX[4], L. B. MERABET[5]; [1]Massachusetts Eye and Ear Infirmary, Boston, MA; [2]Mass. Eye and Ear -- Harvard Med. Sch., Boston, MA; [3]Harvard Med. School, Massachusetts Eye and Ear, Boston, MA; [4]Psychology, Northeastern Univ., Boston, MA; [5]MEEI- SERI Harvard Med. Sch., Boston, MA

Abstract: Background: Visual search of static and dynamic scenes involves higher-order visual processing brain regions. Developmental complications can impair the function of these areas and impact visuospatial performance. Evidence suggests that individuals with cerebral visual impairment (CVI) report difficulties with visual search tasks in complex environments. However, the neural correlates of impaired visual search in this population remain unclear. In this direction, we developed a static and dynamic virtual reality (VR) based visual search task and paired them with electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) respectively.
Methods: A cohort of individuals with CVI (aged 16-25 years) and typically sighted controls (aged 14-28 years) underwent testing. Participants carried out visual search tasks in the static and dynamic VR environments, and were instructed to find a target (an object for the static task and a person in the dynamic task) among varying levels of distractors (i.e. other objects or moving people). Eye movement performance was captured with a Tobii 4C eye tracking system (90 Hz sampling). EEG signals were recorded using a wireless 20-channel system (Neuroelectrics) in response to viewing the static visual search task, and subjects underwent fMRI testing while viewing the dynamic visual search task (3T Philips Achieva system).
Results: Behavioral performance showed marked differences between the control and CVI groups for reaction time and quantified gaze data spread in the static and dynamic tasks. Individuals with CVI; (1) took longer to identify the correct target, (2) had notably wider search patterns, and (3) exhibited further impairment under conditions of higher task complexity, when compared to controls. Additionally, these impairments were more pronounced under the dynamic compared to the static task.

Collected EEG data and static visual search in CVI show (1) delayed timing and (2) differences in magnitude of early ERP brain responses (i.e. n170 and p300). fMRI data and dynamic visual search revealed that CVI participants demonstrated reduced activation in key visual processing regions (i.e., V1, hMT+, FFA, IPS). Furthermore, a pattern of increased frontal activation was observed for the CVI group.
Conclusions: Current results suggest that individuals with CVI have difficulty performing static and dynamic visual search. Increasing visual search demands (i.e. increased distractor levels) had a more detrimental effect in the CVI group. Furthermore, the temporal and spatial aspects of neurological responses within higher order visual processing areas reflected observed behavioral deficits.

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Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.10/A82

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

Title: The role of calcium binding proteins in development of the inner ear

Authors: G. M. FERNANDEZ[1], A. REFAAT[2], T. ABDELHAMID[2], K. M. PEREZ[1], A. MAKLAD[3], *D. R. GIOVANNUCCI[4];
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Abstract: Calcium is an important ion involved in a wide array of physiological processes including regulation of key pathways involved in neuronal development. As such, temporal and spatial calcium dynamics are tightly regulated to accord specificity of signaling during development.In the current study, the vestibular end organs and cochlea were dissected out, incubated with anti-calretinin, anti-parvalbumin, and anti-calbindin antibodies overnight at room temperature and labeled with goat anti-rabbit serum conjugated with Alexa-Fluor 488 for two hours. Following wash, preparations were whole-mounted and examined under confocal microscope. In some preparations, Neuro Vue red nerve tracer was implanted in the vestibular nerve to highlight the brain areas receiving primary vestibular afferents to compare with areas expressing calcium binding proteins and vibratome-sectioned brainstems were then examined by confocal microscopy. At p7, there was robust expression of calretinin protein in all components of the inner ear; the hair cells of the canals' cristae, and in the maculae of the utricle and saccule. The supporting cells, axons neurons in spiral and vestibular ganglia expressed calretinin.

Parvalbumin expression was restricted to the inner hair cells in the basal turn of the cochlea, whereas, in the mid-turn and apical turns the three rows of hair cells expressed parvalbumin. In the vestibular end organs, only type 1 hair cells in the central zone of the cristae and striola regions of the utricle and saccule expressed parvalbumin. Both spiral and vestibular ganglia showed robust expression of parvalbumin. In the brain, calretinin was strongly expressed in the vestibular nuclei, dorsal cochlear nucleus, uvula and nodulus of the cerebellum. Parvalbumin was only expressed in the uvula and nodulus, whereas calbindin was expressed in Purkinje cells of the uvula and nodulus.Our study suggests that all sensory epithelium of the inner ear, including vestibular and cochlear components express at least two of the three calcium binding proteins analyzed. Similarly, all brain areas receiving primary vestibular and primary cochlear afferent express at least one calcium binding protein. We suggest that combinatorial code of the three calcium regulator control early stages of neurogenesis, and axon guidance in the cochleovestibular primary neurons, namely the acquisition of their central and peripheral synaptic targets.

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Poster

460. Development: Sensory and Limbic Systems

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Program #/Poster #: 460.11/A83

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

Support: NSF IOS 165234

Title: Development of serotonergic fibers and and perineuronal nets in the mouse auditory system

Authors: *K. VENABLE, C. C. LEE;
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Abstract: The serotonergic (5-HT) system is a highly conserved neurotransmitter system in mammals, and serotonergic disfunction is implicated in various pathological conditions. The 5-HT system is comprised of multiple receptor subtypes and is involved in crucial aspects of neural development, maintenance, and function, for example neuronal growth and migration, plasticity, and modulation. It is known that serotonin neurons originate in the brainstem and project rostrally and caudally to virtually the entire central nervous system. However, other basic morphological features are yet to be confirmed, e.g. whether serotonin neurons project divergently to multiple levels of the brain (i.e. midbrain and cortex). These features are critical for developing more accurate computational models of auditory processing. Here, we utilized a

mouse model to investigate: (1) the projection patterns and microarchitecture of the serotonergic system through different levels and developmental timepoints in the mouse auditory system, (2) the presence of single divergent 5-HT neurons that project to multiple auditory regions, and (3) the relationship between the serotonin system and perineuronal nets (PNNs). PNNs are critical structures of the extracellular matrix that affect the synaptic plasticity of the neurons they enclose and whose relationship in the auditory system is largely undefined. We utilized immunohistochemical (IHC) detection of serotonin transporters (SERT) and 5-HT for visualizing 5-HT fibers and wisteria floribunda agglutinin (WFA) to detect PNNs at the level of the midbrain to the cortex. Development of these structures were analyzed in male and female C57BL/6J mice at multiple timepoints during postnatal development and adulthood. The association of these structures varies in different auditory regions with age and likely underlies many of the physiological features associated with developing auditory system.

Disclosures: K. Venable: None. **C.C. Lee:** None.

Poster

460. Development: Sensory and Limbic Systems

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

Support: NWO, ALW Open Program grants, no. 819.02.017, 822.02.006 and ALWOP.216
ALW Vici, no. 865.12.001

Title: Oxytocin modulates spontaneous activity patters in the developing sensory cortex

Authors: *P. P. MALDONADO[1], A. NUNO-PEREZ[1,2], J. KIRCHNER[3], E. A. HAMMOCK[4], J. GJORGJIEVA[3], C. LOHMANN[1];
[1]Netherlands Inst. for Neurosci., Amsterdam, Netherlands; [2]Dept. of Fundamental Neuroscience, Fac. of Biol. and Medicine, Univ. of Lausanne, Laussane, Switzerland; [3]Max Planck Inst. for Brain Res., Frankfurt, Germany; [4]Psychology, Florida State Univ., Tallahassee, FL

Abstract: Spontaneous network activity occurs before birth and during early postnatal brain development. Specific patterns of spontaneous activity control the establishment and refinement of central sensory pathways that enable the brain to experience the environment. While neuromodulators and their receptors are highly expressed at this stage of development, it is unclear how they modulate spontaneous activity patterns. By combining *in vivo* and *in vitro*, Ca^{2+} imaging and electrophysiology, we investigated the effect of oxytocin on spontaneous neuronal activity of sensory cortices. Cortical oxytocin application strongly decreased the frequency of spontaneous activity events in the visual cortex (V1), but not in the somatosensory cortex (S1). Furthermore, in V1 oxytocin decreased interneuronal correlations. Voltage-clamp

recordings from layer 2/3 neurons in V1 slices revealed that oxytocin increased the frequency of spontaneous IPSCs but not of EPSCs. In contrast, oxytocin had a balanced effect in S1, increasing the frequency of both IPSCs and EPSCs. Oxytocin-induced inhibition was mediated by the activation of somatostatin$^+$ (SST^+) interneurons, since silencing SST^+ neurons pharmacogenetically blocked this effect fully. In addition, oxytocin specifically depolarized V1 SST^+ interneurons, increased their excitability and affected their action potential features. Thus, oxytocin increases the inhibition/excitation ratio and modulates specific features of V1 spontaneous activity patterns that are crucial for refining developing synaptic connections.

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Poster

460. Development: Sensory and Limbic Systems

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Program #/Poster #: 460.13/A85

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

Support: NIH grant 1R01DC017149-01A1 (Forni, PE)

Title: SMAD4 mediated signaling is required for the precise formation of the vomeronasal somatosensory map to the accessory olfactory bulb

Authors: *A. NAIK[1], E. M. TAROC[2], R. KATREDDI[3], P. E. FORNI[4];
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Abstract: The vomeronasal organ (VNO) contains two main types of vomeronasal sensory neurons (VSNs) that are located in different regions of neuroepithelium namely Apical and Basal. Apical VSNs express receptors of the V1R family of vomeronasal receptors(VR) and project to the anterior AOB, while basal VSNs express receptors of the V2R family and project to the posterior portions of the AOB. The basal neurons selectively express the transcription factors (TF) Tfap2ε while the apical neurons express the TF Meis2. Unlike the olfactory sensory neurons, VSNs expressing the same VR can innervate multiple glomeruli forming homotypic, heterotypic and mixed connections with dendrites of mitral cells in the AOB. What molecular mechanisms control this synaptic specificity remains largely unexplored. Here, we report BMP signaling gradient in the VNO with strong signaling limited to the basal VSNs. SMAD4 is a key player in TGFβ/BMP signaling pathway. By generating SMAD4 conditional knockouts(cKO) we abrogated the pathway in either immature basal VSNs (Tfap2εCRE; SMAD4flox/flox) or in mature VSNs of both populations (OMPCRE; SMAD4flox/flox). We found that conditional

disruption of SMAD4 mediated pathway in immature basal neurons leads to a progressive neuronal cell loss, however, we found SMAD4 mediated signaling to be dispensable once VSNs have reached maturity (OMP). Immunostaining against the presynaptic marker Vglut2, revealed that both models (Tfap2εCRE; SMAD4flox/flox and OMPCRE;SMAD4flox/flox) had significantly fewer and larger glomeruli only in the posterior region of AOB suggesting altered synaptic specificity for the basal VSNs. Transcriptome analysis from both mouse lines revealed misregulation of genes required for synapse organization and maturation. Moreover, immunostaining for immediate early gene cFOS and phosphorylated ribosomal protein S6, after male urine exposure, revealed loss of odor mediated activation of basal VSNs. Our results show, for the first time, a role for BMP signaling in synaptic specificity and functionality and survival of basal VSNs.

Disclosures: A. Naik: None. **E.M. Taroc:** None. **R. Katreddi:** None. **P.E. Forni:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.14/A86

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

Support: NIH Grant R37-HD081168
NIH Grant F32-NS101858

Title: Sensory feedback from myoclonic twitches during active sleep continues to activate sensorimotor structures beyond early infancy

Authors: *J. C. DOOLEY[1], G. SOKOLOFF[3], M. S. BLUMBERG[2];
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Abstract: Myoclonic twitches, which are produced exclusively during active (REM) sleep, occur predominantly in the perinatal period but also persist into adulthood. In rats, sensory feedback from twitches drives neural activity in sensorimotor cortex from postnatal day (P) 2 through at least P12. However, it is not known whether they continue to drive activity in sensorimotor cortex beyond P12. Here, we recorded neural activity in both the forelimb representation of sensorimotor cortex and the ventral posterior nucleus (VP) of thalamus in unanesthetized preweanling rats from P12 through P20. Rats were head-fixed in a device that allowed them to locomote and cycle between sleep and wake. As expected, the quantity of active sleep decreased substantially from P12 through P20. Nonetheless, neurons in both sensorimotor cortex and VP continued to respond to sensory feedback from twitches; they also responded to sensory feedback from wake movements. That twitches drive thalamic and cortical activity

through at least P20 suggests that twitches continue to promote activity-dependent plasticity. In addition, at P16 and P20 but not P12, we observed prolonged periods of high-amplitude theta (5-6 Hz) oscillations in VP that was restricted to periods of active sleep. This thalamic theta may be related to the presence of continuous and coherent theta oscillations during active sleep in the red nucleus, a midbrain motor nucleus that contributes to the production of forelimb twitches, and hippocampus. All together, these findings suggest that active sleep promotes sensorimotor integration beyond the early neonatal period. Ongoing work is focused on such issues as whether theta influences the patterning of twitches and the processing of twitch-related reafference.

Disclosures: J.C. Dooley: None. **M.S. Blumberg:** None. **G. Sokoloff:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.15/B1

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

Support: GM122657
T34GM070387

Title: Exploring the role of microglia and the perineuronal net as effectors of plasticity during barrel cortex development

Authors: A. C. BARRIENTOS[1], S. MROZIUK[2], A. LAHIJANI[2], ***J. C. BRUMBERG**[3]; [1]The Grad. Ctr., New York, NY; [2]Queens Col. , Cuny, Flushing, NY; [3]Queens Col. and The Grad. Center, Cuny, Flushing, NY

Abstract: To understand how tactile experience shapes the brain, it is necessary to study the interaction of the cellular and molecular constituents in the primary somatosensory cortex (S1) during critical period (CP) development. Using the mouse barrel cortex as a model system, we examined two key components in neural development and plasticity: Microglia (MG) and the Perineuronal Net (PNN). In early post-natal development, MG fine-tune the cortical wiring diagram in an experience-dependent manner by strengthening synapses while also removing weak or dying synapses while PNNs mature and emerge at the closure of developmental CPs, restricting plasticity into adulthood. Previously, we demonstrated that by altering the physiological state of MG with pharmacological agents, MG adopt morphological changes that correlate to pathological disturbances, and there is reduction of PNNs. Here, we continue to explore the relationship between MG and the PNN in CP development. C57BL/6 mouse litters underwent trimming in addition to random assignment of IP injections of saline (control), minocycline (a MG inhibitor) and lipopolysaccharide (LPS) to C57BL/6 mouse litters. Pups received chronic injections until post-natal day 30. MG morphology, density and PNN density

were examined using immunohistochemical and histochemical staining and stereology (Neurolucida and Stereo Investigator, MBF). We tested the following hypotheses: (1) trimming coupled with LPS injection will interact synergistically yielding in fewer PNNs, and (2) minocycline injection will synergize with trimming and further reduce PNN density and reduce MG density as it did in minocycline-treated mice with intact whiskers. MG density of trimmed LPS- and minocycline-treated mice do not differ from each other, but they both reduce MG density compared to that of trimmed saline-treated controls. We also report that trimming in conjunction with LPS and minocycline-injection reduce PNN density only in thalamo-recipient layers. A regression analysis shows that greater numbers of MG are related to fewer PNNs. Morphometric analyses of MG show differences between soma features of trimmed minocycline- and LPS-treated mice. Minocycline-treatment results in more complex soma contours and hyper-ramification within MG. Taken together, these studies suggest that sensory deprivation may render the developing brain more vulnerable to factors that influence MG activity and which may be related to PNN development.

Disclosures: A.C. Barrientos: None. **S. Mroziuk:** None. **A. Lahijani:** None. **J.C. Brumberg:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.16/B2

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

Support: NIH Grant MH104780

Title: Disruption of the vomeronasal organ alters mRNA levels of dopamine receptors and steroid-related genes in sexually differentiated brain regions

Authors: *B. JACKSON[1], A. SWIFT-GALLANT[2], M. BREEDLOVE[1], C. JORDAN[1]; [1]Michigan State Univ., East Lansing, MI; [2]Psychology, Mem. Univ. of Newfoundland, St. John's, NL, Canada

Abstract: Mate preference in mice is profoundly affected by the disruption of pheromonal processing by the vomeronasal organ (VNO) when the signaling molecule “transient receptor potential cation channel” (Trpc2) is knocked-out. These knockout (KO) males readily mount same-sex partners and fail to display male-typical aggressive behaviors. KO females display male-typical sexual behaviors such as vigorous mounting towards both same and opposite-sex partners, and significantly reduced maternal aggression. These findings are striking given the well-established role of gonadal hormones in organizing such behaviors. Here, using real-time qPCR, we assessed whether Trpc2-KO males and females differ from same-sex wildtype (WT)

mice in mRNA levels of sex hormone receptors and dopamine receptors (DR) in the vomeronasal olfactory pathway. We find differences in estrogen receptors (ESR1 and ESR2) mRNA in the ventromedial hypothalamus (VMH), and nucleus accumbens (NA) in KO males compared to WT males. KO females show a downregulation of aromatase (Arom) and DR2 in the medial preoptic area (MPOA), and upregulation of DR2, DR3 and DR4 in the VMH compared to WT females. However, the most remarkable differences were that sex differences between KO males and KO females were exaggerated compared to WT males and WT females; while WT males and females differ in Arom mRNA in the bed nucleus of stria terminalis (BNST), medial amygdala and VMH, KO males and females also differ in DR1-5 and ESR2 in the NA, Arom in MPOA, ESR1 in BNST, and ESR1, DR2 and DR3 in VMH. These results suggest that impaired VNO functioning alters hormone and dopamine sensitivity in the vomeronasal olfactory pathway, which may contribute to the behavioral differences observed in Trpc2 KO mice.

Disclosures: B. Jackson: None. **A. Swift-Gallant:** None. **M. Breedlove:** None. **C. Jordan:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.17/B3

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

Title: Role of Kiss1r in the cellular development of tongue of puberal Wistar rats

Authors: *A. M. JACINTO[1], A. MOLINA[1], B. PAIZ[1], V. ALATRISTE[2];
[1]Ctr. De Investigación Y Estudios Superiores En E, Puebla, Mexico; [2]BUAP, Puebla, Mexico

Abstract: The tongue is an organ that participate in important functions such as chewing, swallowing, language and sense of taste. In tongue, the cell development is regulated by several nervous fibers, growth factors, hormones, and others than nociceptive fibers that are not fully understood. Our objective was to study the role of Kiss1R in the epitheliums of tongue. We used 3 groups of rats, control, vehicle and treated with Kisspeptin-234 trifluoroacetate salt (p-234) 10 nM, n=5 for each group. At age of P24 by a surgical procedure, we injected vehicle (I.S.S. 100 µl) or p-234 (10 nM/ 100 µl of I.S.S.) in each horn of the uterus. Next we determinate the onset of puberty (FVO) when the vagina were completely open. For control, we only determinate the FVO. At the FVO we sacrificed the animals by CO_2 exposure and then we obtained the tongues. The tongues were fixed, and histologically treated to obtain 5 µm slides by microtome. Then some slides were stained with hematoxylin and eosin to determinate the changes in the different epitheliums, other slides were stained with Mason Trichromic to evaluate the connective tissue and finally we located the Kiss1r in the tongues by Immunohistochemestry. Our results show

that the inhibition of Kiss1r produces changes in the level of development of tissues such as mucous but not serous acini, muscle tissue, dorsal epithelium (germinative filiform papillae, lingual tonsils, filiform papillae and fungiform papillae) and the ventral epithelium (stratified smooth). And also, we determinate than there are differences in the Kiss1r expression in the vehicle and p-234 treated rats. We propose that Kiss1r participate in the development of the tissue probably through the regulation of nociceptive pathways.

Disclosures: **A.M. Jacinto:** None. **A. Molina:** None. **B. Paiz:** None. **V. Alatriste:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.18/B4

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

Support: NIH R01 DA044925

Title: Inhibition of ventral tegmental area dopamine neurons rescues aberrant locomotor activity induced by prenatal cannabis exposure in male offspring

Authors: *S. ARONI[1], R. FRAU[2], M. MELIS[3], J. F. CHEER[4];
[1]Univ. of Maryland, Sch. of Med., Baltimore, MD; [2]Univ. of Cagliari, Cagliari, Italy; [3]Univ. of Cagliari, Monserrato, Italy; [4]Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Epidemiological studies report that prenatal cannabis exposure (PCE) increases the risk of developing schizophrenia in adulthood. Moreover, PCE predisposes to behavioral and cognitive deficits including hyperactivity, enhanced impulsivity, loss of sustained attention and increased sensitivity to drugs of abuse. These neuropsychiatric impairments are associated with dopaminergic signaling dysfunction, a phenomenon common in schizophrenic patients. However, the mechanisms through which PCE alters brain development leading to the manifestation of neuropsychiatric disorders are still unclear. Hence, we hypothesized that PCE induces behavioral dysfunction by enduringly altering the mesolimbic dopaminergic system. Long Evans dams expressing cre recombinase under the control of the TH promoter (TH::Cre) received Δ^9-tetrahydrocannabinol (THC) or vehicle (2 mg/kg/ml, daily) from gestational day 5 (GD5) to GD20. This low dose of THC does not elicit tolerance after repeated administration. A novel open field test was performed in male offspring at postnatal day 27-28 (PND27-28), corresponding to human pre-adolescence, under basal conditions and after an acute administration of THC (2.5 mg/kg/2 ml). Next, we evaluated the role of mesolimbic dopamine (DA) transmission by injecting a cre-dependent adeno-associated virus expressing an inhibitory DREADD (AAV5-DIO-hM4D(G_i)-mCherry) to target DA neurons in the ventral tegmental area

(VTA) of TH::Cre positive offspring. Open field testing was performed 30 minutes following systemic administration of clozapine-N-oxide (CNO, 3 mg/kg/2 ml i.p.) to activate VTA G_i-DREADDs . No differences were observed in spontaneous locomotor activity between vehicle and PCE offspring unless they were challenged with THC. Notably, acute THC paradoxically heightened the total distance traveled and the velocity (as opposed to canonical hypolocomotor response induced by acute THC) in PCE rats. Remarkably, THC-induced hyperlocomotion was curtailed in animals injected with G_i-DREADDs. These data suggest a causal involvement of VTA DA neurons in the paradoxical hyperlocomotor response to THC in PCE rats. Our findings improve the knowledge about the complex neurobiological processes underlying the pathophysiology of PCE-induced psychiatric disorders. We are currently running *in vivo* fiber photometry, to measure *nucleus accumbens* (NAc) DA transients in PCE-exposed adult animals, in order to further investigate the PCE-induced mesolimbic DA system disruption and the risk to develop compulsive drug-seeking behavior in adulthood.

Disclosures: S. Aroni: None. **R. Frau:** None. **M. Melis:** None. **J.F. Cheer:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.19/B5

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

Support: NIMH R01MH105447

Title: Examining the effects of early life SSRI antidepressant exposure on hippocampal metabolism and morphology

Authors: *K. A. UNROE[1], M. E. GLOVER[2], E. A. SHUPE[2], C. R. MCCOY[2], S. M. CLINTON[2];
[1]Translational Biology, Medicine, and Hlth., [2]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Selective serotonin reuptake inhibitor (SSRI) antidepressants are commonly prescribed to treat pregnant and postpartum women suffering from depression. While SSRIs are generally considered safe to use in pregnancy, growing evidence shows that *in utero* SSRI exposure can elicit detrimental effects on offspring's emotional health, including increasing risk for depression. Rodent studies support these findings, showing that early life exposure to SSRIs alters brain development and leads to increased adult depression-like behavior. Work in our laboratory found that perinatal SSRI exposure triggered changes in DNA methylation and gene expression in the early postnatal hippocampus, with numerous alterations occurring in genes involved in neurodevelopment, metabolism, and synaptic plasticity. Based on these findings, we now hypothesize that perinatal SSRI exposure alters hippocampal circuit formation through

changes in dendritic spines and/or metabolic activity. To test this idea, we treated adult female Sprague Dawley rats with the SSRI citalopram (10 mg/kg/day) in drinking water (or vehicle - tap water) throughout pregnancy and the three-week postpartum period. Brains were harvested from male and female offspring at two developmental time points - postnatal day (P)14 when prominent perinatal SSRI-induced molecular changes were previously found and P75 when behavioral abnormalities are observed. A subset of the brains were processed for Golgi-Cox staining to evaluate dendritic spine density in subregions of the hippocampus (Cornu Ammonis, CA and dentate gyrus) of perinatal SSRI-exposed and control offspring. The remaining brains were processed for a histochemical assay to measure the activity of cytochrome c oxidase (COX), a proxy for basal metabolic activity. Our initial COX activity analysis focused on subregions of the hippocampus, but we later extended the assessment to the prefrontal cortex, habenula, and nucleus accumbens to test whether perinatal SSRI exposure affected metabolic activity beyond the hippocampus. Our results so far show that early life SSRI exposure increases COX activity in the adult male and female CA hippocampus and dentate gyrus. Ongoing analyses will determine whether these changes occur at earlier time points and whether other brain regions are affected. Likewise, the ongoing dendritic spine studies will test whether perinatal SSRI-related metabolic changes are associated with concomitant alterations of dendritic spine density and/or morphology. Together, these data will provide important information regarding the impact of perinatal SSRI exposure on brain development and emotional behavior.

Disclosures: K.A. Unroe: None. **M.E. Glover:** None. **E.A. Shupe:** None. **C.R. McCoy:** None. **S.M. Clinton:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.20/B6

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

Support: NIH Grant NS064135

Title: Multimodal identification of molecular layer neurons in the mouse hippocampal formation

Authors: *M. ANSTÖTZ[1], G. MACCAFERRI[2];
[2]Dept Physiol, [1]Northwestern Univ., Chicago, IL

Abstract: Information originating from the entorhinal cortex reaches the hippocampus via layer specific projections that reach the molecular layers. Here local circuits composed by GABAergic interneurons (INs) and glutamatergic Cajal-Retzius cells (CRs) integrate entorhinal input and produce physiologically-meaningful signaling. Therefore, the properties of specific and different types of local neurons in the molecular layers are important determinants of hippocampal

computations.
Unfortunately, several studies are based on a mistaken identification of the cells studied. For example, they often miss the important fact that the hippocampal molecular layers of adult rodents still contain CRs and consider every cell of the molecular layer as INs or, alternatively, they misidentify reelin-expressing INs for CRs by not considering that reelin is not a univocal molecular marker.
Here, we try to provide clear methodological criteria to allow an unambiguous distinction between these two different cell types.
First, we have used transgenic reporter mice and immunohistochemical experiments to show distinct spatio-temporal dynamics of these two neuronal populations. CR-cells appear clustered with a strong decrease in density during development. In contrast INs displayed a spatio-temporally homogenous distribution. Second, we have evaluated a series of molecular markers such as reelin, calretinin, CoupTF2, and p73 by quantifying the specificity of expression in both populations.
Third, we have used combined patch-clamp electrophysiology and post-hoc structural reconstructions to reveal key morphological parameters that could lead to the distinction of INs from CRs.
Lastly, we have taken advantage multivariate analysis to produce a clear and specific identification of distinct neuronal populations such as INs and CRs.
We hope that our new results and methodology will help avoid future ambiguity and potential mistakes in cellular investigations of the molecular layers.

Disclosures: **M. Anstötz:** None. **G. Maccaferri:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.21/B7

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

Support: NIH Grant 2R01DA020140

Title: Foxp2 dependent formation of the social brain and sex specific function in social behaviors

Authors: *L. WANG[1], M. J. HERRERO[1], M. GOODRICH[1], T. SASAKI[1], C. LAZARSKI[2], Y. IMAMURA[3], A. PANIGRAHI[2], N. A. SMITH[1], K. HASHIMOTO-TORII[1], J. G. CORBIN[1]; [1]Ctr. for Neurosci. Res., [2]Ctr. for Cancer Immunol. Res., Children's Natl. Med. Ctr., Washington, DC; [3]Genome Sci. and Bioinformatics Core, Penn State Col. of Med., Hershey, PA

Abstract: The *Foxp2* gene encodes a transcription factor that is expressed in a variety of brain regions including the cerebral cortex, striatum, cerebellum and the amygdala. *Foxp2* is required for a variety of developmental processes including neuronal specification and dendrite formation. *Foxp2* mutations in humans are associated with language deficits and autism. One region of high expression of *Foxp2* is the medial subnucleus of the amygdala (MeA), which is involved in the regulation of social behaviors such as reproduction and defense. Our previous studies have revealed that Foxp2+ neurons in the MeA are a subclass of inhibitory output neurons and are activated in a sex-specific manner during mating and aggressive behaviors (Lischinsky et al., *eLife*, 2017). Based on these findings, we hypothesized that *Foxp2*-lineage neurons in the MeA express cohorts of genes/proteins involved in social behaviors and function in specification of neuronal circuits regulating social behaviors. To test this hypothesis, we first assessed expression of genes via biased and unbiased approaches in *Foxp2*-lineage neurons at both embryonic and postnatal stages. We further assessed *Foxp2*-lineage responses to application of different neuromodulators known to act in the MeA. We then conducted a wide battery of behavioral assessments in male and female *Foxp2+/-* mutant mice, including 3-chamber social interaction, olfactory discrimination, mating assays, resident-intruder aggression, predator odor aggression and maternal aggression. We found that *Foxp2+/-* mice displayed impaired social interaction and olfactory discrimination behaviors in a sex-specific manner. Correlating with these behavioral deficits were alterations in protein expression in the *Foxp2+/-* MeA. Thus our current results suggest that *Foxp2* may activate sex-specific genetic programs to regulate sex-specific social behaviors, which could help to better understand amygdala-linked and sex-biased developmental disorders, such as autism.

Disclosures: L. Wang: None. **M.J. Herrero:** None. **M. Goodrich:** None. **T. Sasaki:** None. **C. Lazarski:** None. **Y. Imamura:** None. **A. Panigrahi:** None. **N.A. Smith:** None. **K. Hashimoto-Torii:** None. **J.G. Corbin:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.22/B8

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

Support: NSFC 81771225

Title: Establishment of a mouse model carrying mutant DDP1 gene

Authors: *Y. HU, P. SONG;
Nanfang Hosp., Guangzhou, China

Abstract: Deafness-Dystonia-Optic Neuropathy (DDON) Syndrome, also known as Mohr-Tranebjaerg Syndrome (MTS; MIM 304700), is a rare progressive X-linked recessive disorder characterized by deafness, dystonia or ataxia and reduced visual acuity. *DDP1* (Deafness/Dystonia Peptide 1), which is also named as *TIMM8A* (Translocase of Inner Mitochondrial Membrane 8A) is the only causative gene. However, no DDON disease model mouse has been established and the molecular mechanism is still unclear. In the present study, we characterized a DDON patient with a novel hemizygous variation in *DDP1/TIMM8A* gene (NM_004085.3): c.82C>T (p. Q28X). Further, based on this variant, we generated a mouse line carrying hemizygous variation in *DDP1/TIMM8A* by clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 technology. *DDP1*$^{I23fs49X/y}$ mutant male mice exhibited reduced body weight, elevated hearing threshold, impaired learning ability, reduced forelimb grip strength, and impaired pain perception at early ages. However, balance and motor coordination and visual acuity were unaffected in mutant mice. On the molecular basis, immunofluorescence and electron microscopic analysis showed the distribution of variant DDP1 proteins (DDP1 Q28X or DDP1 I23fs49X) were changed. Variant DDP1 made mitochondria appeared rounder and swollen with broken cristae, especially in the primary auditory cortex (Au1) of mutant mice. In addition, Western blot analysis showed reduced levels of DDP1 do not affect biogenesis of mitochondrial oxidative phosphorylation system (OXPHOS) protein and soluble matrix protein SOD-2. Taken together, we have successfully generated the a first mouse model with DDP1 gene frame shift mutation , which recaptured many symptoms or signs of DDON syndrome. DDP1 variations result in changes in the localization and mitochondrial morphology.

Disclosures: **Y. Hu:** None. **P. Song:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.23/B9

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

Support: PROMEP/103.5/12/4857
PROFOCIE UCOL-CS 2015.2017

Title: Dose dependent anxiogenic effect of levetiracetam during pregnancy on an epilepsy model in Wistar rats and its relationship with SV2A in hippocampus of the offspring

Authors: *M. F. PINTO-GONZÁLEZ[1], N. A. MOY-LÓPEZ[1], J. GUZMÁN-MUÑIZ[1], N. Y. CORTÉS-ÁLVAREZ[1], O. P. GONZÁLEZ-PÉREZ[1], J. L. COLLÁS-AGUILAR[1], C. M. GAITÁN-VAZQUEZ[2], M. FLORES-RAMIREZ[3];

[1]Lab. of Neurosci., Univ. of Colima, Colima, Mexico; [2]Univ. del Valle de Atemajac, Colima, Mexico; [3]Fac. of Medicina, Univ. de Colima, Colima, Mexico

Abstract: During pregnancy, both maternal epilepsy and classic anticonvulsive use may have teratogenic effects over the development of the central nervous system. By other hand, use of new generation anticonvulsive drugs, as Levetiracetam (LEV) may be a safe option for seizure control during pregnancy without affecting the development of the progeny, such as changes in the expression of synaptic vesicle protein 2A (SV2A), LEV binding site. Our aim was to analyze the anxiogenic effect of growing doses of LEV during pregnancy on an epilepsy model and its relationship with SV2A expression in the hippocampus of the offspring. 12 nulliparous female rats at 90 days of age were divided in 6 groups with different conditions: 1) negative control, saline solution (SS); 2) Positive control LEV 25 mg/kg in SS (LEVSS); 3) LEV 25 mg/kg with previous exposition to Picrotoxin (LEV25); 4) 50 mg/kg LEV-PTX (LEV50); 5) 100 mg/kg LEV-PTX (LEV100); and 6) Exposure to PTX with SS only (PTX). 1.5 mg/kg of PTX or saline solution for 10 days were given for the epilepsy model. Resulting female and male pups were considered as the study subjects (n=120, 20 per group). Anxiety evaluation was made on P42 using the elevated plus maze (EPM), results from EPM were analyzed by anxiety index. To see if there was an effect over mobility, open field test was also applied to identify changes in total distance moved and speed. Tissue was obtained also in P42 to measure Hippocampal expression of SV2A by immunohistochemistry and evaluated with optic density. According to data normality, Kruskall-Wallis was applied. Results from the anxiety index showed significant differences according to treatment ($H=11.526$, $gl=5$, $p=0.009$), while posterior contrast analysis showed that LEVSS group presented a decreased anxiety index compared with control group (SS). By other hand, mobility also showed significant differences in distance traveled ($H=9.276$, $gl=5$, $p=0.026$), and velocity ($H=9.211$, $gl=5$, $p=0.027$), which in the contrast analysis were also related to differences between SS and LEVSS groups, having LEVSS pups an increased mobility compared to SS. There were no differences between control group and the ones with other conditions in behavioral test. While in SV2A hippocampal expression, there was no statistical difference between control group and those who were administered LEV, PTX group showed a significant increased SV2A expression in C3 and DG areas, compared with the rest of the groups ($p<0.05$). Results suggest that LEV exposure during critical periods of brain development without PTX exposure may lead to an anxiolytic effect, while preventing changes on SV2A expression when dams are previously exposed to a PTX epilepsy model.

Disclosures: **M.F. Pinto-González:** None. **N.A. Moy-López:** None. **J. Guzmán-Muñiz:** None. **N.Y. Cortés-Álvarez:** None. **O.P. González-Pérez:** None. **J.L. Collás-Aguilar:** None. **C.M. Gaitán-Vazquez:** None. **M. Flores-Ramirez:** None.

Poster

460. Development: Sensory and Limbic Systems

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Program #/Poster #: 460.24/B10

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

Support: NIMH/NIH R01 MH105447

Title: Early life exposure to the SSRI citalopram alters limbic expression of Brain-specific angiogenesis inhibitor 3 (Bai3) and associated ligands in a sex-dependent manner

Authors: *E. A. SHUPE[1], M. E. GLOVER[1], K. A. UNROE[2], S. M. CLINTON[1];
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Abstract: Selective Serotonin Reuptake Inhibitors (SSRIs) are the mainstay antidepressant treatment for the 10-20% of pregnant and postpartum women who suffer from major depression. Although maternal antidepressant use is considered generally safe, producing minimal risk for pregnancy complications or teratogenic effects, *in utero* exposure may elicit enduring effects on neurodevelopmental and neuropsychiatric outcomes in the offspring. Clinical and basic scientific research both suggest that early-life SSRI exposure may increase risk of depression in adulthood. Consistent with clinical findings, studies in rodents demonstrate that perinatal exposure to SSRIs disturbs multiple behavioral domains relevant to depression, contributing to increased anhedonia, behavioral despair, and anxiety. Recent data by our laboratory have replicated these findings to show that perinatal citalopram exposure increases anhedonia and behavioral despair in both male and female adult rat offspring. In addition, our laboratory has demonstrated that signaling of Brain-specific angiogenesis inhibitor 3 (Bai3), an adhesion G-protein coupled receptor involved in regulating synaptogenesis and dendritic spine formation, is altered by perinatal exposure to multiple SSRIs in rats. The present study tests the working hypothesis that perinatal exposure to the SSRI citalopram alters neurodevelopmental and behavioral outcomes in part through disruptions in Bai3 signaling. To test this, we examined mRNA expression of Bai3 and associated signaling molecules, including C1ql1-3 and Elmo2, during early development (postnatal day (P)14) and in adulthood (P60) in limbic brain regions of male and female rat offspring exposed to the SSRI citalopram from gestation through weaning. At P14, expression of the Bai3 ligand C1ql3 in the dorsal CA of the hippocampus is increased in female, but not male, offspring exposed to citalopram. By P60, C1ql3 expression in control female offspring is elevated relative to male offspring, but female perinatal SSRI-exposed offspring show decreased levels compared to control females. Further, in the prefrontal cortex, Bai3 and C1ql3 expression are enhanced in perinatal SSRI-exposed female, but not male, offspring at P14, an effect which does not persist at P60. Altogether, these findings raise important considerations for the use of SSRIs during pregnancy and suggest a possible role of the Bai3 signaling pathway in the

etiology of depression-like behavior in SSRI-exposed offspring, as functional changes during development in limbic structures including the hippocampus likely contribute to increased vulnerability for depression in adulthood.

Disclosures: E.A. Shupe: None. **M.E. Glover:** None. **K.A. Unroe:** None. **S.M. Clinton:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.25/B11

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

Title: Small molecules to correct the alternative splicing of human mutant ELP1 transgene in mouse models of familial dysautonomia

Authors: *X. ZHAO[1], J. NARASIMHAN[1], A. DAKKA[1], V. GABBETA[1], S. JUNG[1], A. MOLLIN[1], N. ZHANG[1], J. WANG[1], S. ZHANG[1], E. MORINI[2], P. DIETRICH[3], M. SALANI[2], I. DRAGATSIS[3], S. A. SLAUGENHAUPT[2], G. KARP[1], N. A. NARYSHKIN[1], M. WEETALL[1];
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Abstract: Introduction: Familial dysautonomia (FD) is an autosomal recessive inherited disorder of the nervous system that affects the development and survival of autonomic and some sensory neurons. Originally reported by Riley et al in 1949, FD is now recognized as one of several hereditary sensory and autonomic neuropathies. More than 98% of patients have been of Ashkenazi Jewish descent.
FD is caused by a mutation that results in a change in the mRNA splicing mutation resulting in the tissue-specific skipping of exon 20 and a corresponding reduction of the Elongator complex protein 1 (ELP1).
Methods and Results: Through chemical screening and optimization, we identified orally available small molecules that correct the ELP1 mRNA splicing resulting in full-length mRNA. These compounds are able to increase full length ELP1 mRNA and ELP1 protein in patient fibroblasts . Oral administration of these compounds to mice that express the human mutant ELP1 transgene, led to an increase in ELP1 protein in multiple PNS and CNS tissues in a dose dependent manner .
A phenotypic mouse, TgFD9; ELP1Δ20/flox carries the human mutant IKBKAP transgene and expresses extremely low levels of endogenous ELP1 (ELP1Δ20/flox). It recapitulates many phenotypic features and same tissue-specific mis-splicing defect seen in FD patients, including reduced growth rate, reduced number of fungiform papillae, spinal abnormalities, sensory and sympathetic impairments .

We hypothesized that a small level of ELP1 elevation during the early development in brain or in peripheral nerve system may lead to phenotypic improvements in our animal models. We observed that TgFD9; ELP1Δ20/flox have a reduced birth rate (less than the expected ratio). We found that ELP1Δ20/Δ20 mice, expressing less ELP1 protein resulted in 100% embryonic lethality. On the contrary, the survival of a milder line (TgFD9; ELP1flox/flox) was close to 100% and achieved almost normalized body weight. The correlations between total ELP1 and survival and phenotypic severities in these mice will be needed for further investigations. Conclusions: Small molecule splicing modifiers of the human mutant ELP1 mRNA associated with FD have shown efficacy in both cellular and animal models of familial dysautonomia.

Disclosures: **X. Zhao:** None. **J. Narasimhan:** None. **A. Dakka:** None. **V. Gabbeta:** None. **S. Jung:** None. **A. Mollin:** None. **N. Zhang:** None. **J. Wang:** None. **S. Zhang:** None. **E. Morini:** None. **P. Dietrich:** None. **M. Salani:** None. **I. Dragatsis:** None. **S.A. Slaugenhaupt:** None. **G. Karp:** None. **N.A. Naryshkin:** None. **M. Weetall:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.26/B12

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

Support: NIEHS CEHSCC Pilot Grant UWM
UWM SURF Award

Title: Defects in visual behavior and jaw morphology are associated with reduced growth and survival in Cabin1 knockout zebrafish

Authors: *S. C. SARICH[1], R. CRUZ[1], M. N. ISTIBAN[1], W. MAHMOUD[1], H. MARTINEZ RAMIREZ[1], H. N. WATERS[1], J. E. EXLINE[1], J. MATHIAPARANAM[2], B. A. LINK[3], M. A. WOLMAN[2], A. J. UDVADIA[1];
[1]Biol. Sci., Univ. of Wisconsin Milwaukee, Milwaukee, WI; [2]Integrative Biol., Univ. of Wisconsin, Madison, WI; [3]Med. Col. of Wisconsin, Milwaukee, WI

Abstract: Cabin1, an inhibitor of calcineurin and MEF2 activity, is enriched in developing neurons and neural crest tissues. Previously we discovered that knockdown of Cabin1 gene expression resulted in diminished sensorimotor responses and craniofacial abnormalities. To further validate our preliminary findings, we have established zebrafish strains with Cabin1 gene knockout using CRISPR/Cas9 genome editing. In the knockout strains, we recover half of the expected rate of Cabin1 homozygous mutants based on Mendelian inheritance, with the loss occurring during larval stages. Furthermore, the surviving mutants are significantly smaller in size than their wild type and heterozygous siblings. Behavioral testing of mutant fish revealed a

specific defect in response to visual stimuli. As previously observed in the Cabin1 knockdown fish, Cabin1 homozygous mutants also display abnormal jaw morphology. We are currently testing the hypothesis that defects in visual behavior and jaw morphology impact feeding capability, ultimately leading to the observed decrease in larval growth and survival.

Disclosures: S.C. Sarich: None. **R. Cruz:** None. **M.N. Istiban:** None. **W. Mahmoud:** None. **H. Martinez Ramirez:** None. **H.N. Waters:** None. **J.E. Exline:** None. **J. Mathiaparanam:** None. **B.A. Link:** None. **M.A. Wolman:** None. **A.J. Udvadia:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.27/B13

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

Support: NIH/NEI grant R00 EY023995
REU site award DBI-1659347

Title: Developing a modifier screen for novel regulators of the hippo tumor suppressor pathway in *Drosophila*

Authors: *W. R. MEARA, J. RISTER;
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Abstract: Carefully regulated gene expression creates an enormous variety of neurons. Signaling pathways are often repurposed to differentiate sensory neurons, however the mechanistic details of this process are not fully understood. One example is the highly conserved Hippo tumor suppressor pathway, which is used to differentially express color sensitive Rhodopsin (Rh) proteins in a subset of Drosophila photoreceptors. This results in a mutually exclusive decision to either express blue-sensitive Rh5 (~35%) or green-sensitive Rh6 (~65%). Reuse of the Hippo pathway in photoreceptors offers an exciting new context to screen for tumor suppressors and growth regulators using the binary readout of Rh5 (Hippo off) vs. Rh6 (Hippo on). We established a paradigm to identify genotypes with abnormal Rh5:Rh6 ratios in a high throughput manner using water immersion microscopy and an Rh5>gfp reporter. We have found multiple genotypes that exhibit increased or decreased ratios of Rh5:Rh6 that can serve as genetic backgrounds in modifier screens for novel Hippo regulators. We also discovered an Rh6 derepression phenotype that was analyzed using complementation tests. These findings will further our understanding of the Hippo pathway and photoreceptor differentiation.

Disclosures: W.R. Meara: None. **J. Rister:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.28/B14

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

Support: McDonnell Foundation

Title: Alterations in patterns of gene expression in the Brazilian short-tailed opossum (Monodelphis domsetica) due to early loss of vision

Authors: *M. ENGLUND[1], R. T. BOTTOM[2], R. F. PEREZ, JR[2], K. J. HUFFMAN[3], D. S. STOLZENBERG[1], L. A. KRUBITZER[4];
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Abstract: Spontaneous activity from the periphery and experience-dependent mechanisms work in concert during development to generate the functional organization and connectivity of the neocortex. Early loss of sensory input dramatically alters how this developmental program unfolds. To study the effects of vision loss, we used the Brazilian short-tailed opossum (Monodelphis domestica), which has a well-developed visual cortex and is highly altricial at birth. Previous work in our laboratory has shown that when visual input is lost very early in development, neurons in would-be visual cortex respond to somatosensory and auditory stimulation. In addition, V1 receives input from both the primary auditory (A1) and the primary somatosensory (S1) areas. To appreciate how the developmental program is altered to produce these observed changes, we bilaterally enucleated opossums at postnatal day (P) 4, prior to the onset of spontaneous retinal activity and before thalamocortical axons have reached the cortex. We then took micropunches from V1 and S1 just after eye opening at P36, when experience-dependent pruning of visual cortex is underway, and used qPCR to test for differences in gene expression levels within fields, and in-situ RNA hybridization (ISH) to assess expression patterns across the cortex. Data from qPCR experiments show that experimental P36 animals enucleated at P4, have significant decreases in the expression of patterning genes within the region corresponding to visual cortex in controls. These genes, Id2 and RZRβ, are involved in areal and laminar patterning and regulate the development of intraneocortical connections. Additionally, we observed a relative reduction in GABAa receptor and Ephrin A5 expression in V1 of early blind animals. Utilizing our newly developed in-house, Python based toolbox for quantifying gene expression gradients across the entire cortex from raw ISH data, we found that the expression of Id2 and RZRβ were shifted medially in P36 animals enucleated at P4 compared to control P36 animals. Futhermore, lateral to the V1/V2 boundary, Id2 expression was significantly increased in P36 animals enucleated at P4 compared to sighted controls.

Interestingly, this heightened expression co-registers with the previously defined 'Area X,' a heavily myelinated region observed in adult early blind animals. In sum, our data suggests that the early loss of vision results in cortex-wide alterations to gene expression patterns in areas that process both the spared and lost senses.

Disclosures: M. Englund: None. **R.T. Bottom:** None. **R.F. Perez:** None. **K.J. Huffman:** None. **L.A. Krubitzer:** None. **D.S. Stolzenberg:** None.

Poster

460. Development: Sensory and Limbic Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 460.29/B15

Topic: A.04. Transplantation and Regeneration

Support: NIH RO1-DC01426
Schmitt Program on Integrative Neuroscience
UR Ventures

Title: ErbB2 signaling drives cochlear supporting cell and GER cell proliferation *in vitro* and hearing improvement after noise *in vivo*

Authors: *J. ZHANG[1], L. SHAH[1], J. LIU[2], K. S. HENRY[3], P. WHITE[1];
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Abstract: Hearing is the ability to detect and perceive sound, an important quality in human activities. Hearing loss follows when cochlear hair cells (HCs) are damaged or lost due to various factors, such as ototoxic insults and exposure to noise. In mammals, HCs are not regenerated once they die, resulting in permanent hearing impairment. Moreover, some insults drive hearing loss even though HCs persist, suggesting cochlear dysfunction. Here we report on the effects of expressing constitutively activated ERBB2 receptors (CA-ERBB2) in mouse cochlear SCs. We used a Tet-On transgenic strategy to achieve ERBB2 gain-of-function at different stages.
Perinatally, CA-ErbB2 activation in cochleae can be accomplished by crossing a Tet-On CA-ErbB2 line with an inner ear specific rtTA line, Sox10-rtTA. Such expression is under temporal control by doxycycline application to cochlear culture from postnatal age day 2 (P2). Significant proliferation was observed in SCs and in the cochlear greater epithelial ridge (GER) region upon CA-ErbB2 activation. HC damage in combination with CA-ERBB2 treatment may deliver different effects, which are under investigation both *in vivo* and *in vitro*.
In young adults, we adopted a similar transgenic approach to activate CA-ErbB2 in SCs. To assess the potential therapeutic effects from CA-ERBB2, we exposed mice with strong noise,

consisting of an 8-16 kHz band at 110 dB for two hours. This noise exposure drove temporary thresholds shifts of an average of 30 dB and permanent threshold shifts of 25 dB across all auditory frequencies. Here we report significantly improved auditory thresholds in mice that endured such level of noise but were treated with CA-ERBB2 expression in their cochlear SCs. Cochlear HCs, as the primary sound transducers, were largely preserved in both control and CA-ERBB2 groups. Synapses between HCs and auditory nerves, the connecting parts from the cochlea to the brain, are currently under investigation.
Previous studies suggested the potential roles of EGF family ligands in promoting regeneration. We report that the expression of a constitutively active receptor, ERBB2, involved in this signaling pathway correlates with proliferation in cochlear SCs at early stage and improved hearing after noise damage at young adulthood. The underlying mechanisms for this improvement will be the focus of future study.

Disclosures: **J. Zhang:** None. **L. Shah:** None. **J. Liu:** None. **K.S. Henry:** None. **P. White:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.01/B16

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH Grant MH083928
NIH Grant DA041673

Title: Kappa-opioid receptor regulated dopamine clearance is linked to dopamine transporter phosphorylation

Authors: ***S. RAMAMOORTHY**[1], D. RAGU VARMAN[1], A. E. MORITZ[2], R. HORTON[3], M. VITELA[3], L. C. DAWS[3], J. D. FOSTER[2], L. D. JAYANTHI[1], R. A. VAUGHAN[2], T. SHIPPENBERG[4];
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Abstract: Dynorphin (DYN), its receptor, the kappa opioid receptor (KOR), and mesolimbic dopamine (DA) neurotransmission systems are implicated in the pathogenesis of depression and addiction. DYN-fibers synapse onto DA terminals, and KOR are expressed on these same DA terminals. This anatomical co-presence of Dyn/KOR structures on DA neurons suggests that the presynaptic DYN/KOR system may modulate DA transmission. Indeed, KOR agonists decrease

DA release and extracellular DA concentrations. Effective clearance of released DA from the extracellular space by the DA-transporter (DAT) is one of the critical factors regulating dopaminergic neurotransmission. Previously, we demonstrated that KOR agonists upregulate DAT activity by increasing surface DAT expression through extracellular signal-regulated kinase1/2 activation (ERK1/2) (PMC4188751). DAT is a phosphoprotein, and whether DAT phosphorylation is involved in KOR- mediated DAT regulation and trafficking is unknown. In the current study, we investigated the role of DAT phosphorylation in mediating acute KOR regulation of rat DAT (rDAT). KOR agonist U69,595 increased DAT activity in cells coexpressing KOR and rDAT. We discovered that the N-terminal region (amino acids 23-55) of rDAT is involved in KOR-mediated rDAT upregulation. Immunoblot studies using a phosphoThr53-DAT antibody revealed that U69,593 treatment stimulated Thr53 phosphorylation of rDAT in cells coexpressing KOR, which was blocked by the KOR antagonist nor-binaltorphimine (nor-BNI). U69,593 mediated Thr53 phosphorylated rDAT was predominantly found on plasma membrane-resident rDAT. Mutation of Thr53 to Ala53 in rDAT prevented U96,593/KOR-enhanced DAT activty and Vmax, as well as surface expression and phosphorylation. Increased Thr53 phosphorylation of native rDAT was observed in rat nucleus accumbens and caudate putamen following systemic administration of KOR agonist U69,593. Furthermore, *in vivo* high-speed chronoamperometry studies demonstrate that while KOR-agonist U69,593 accelerate DA clearance, KOR-antagonist nor-BNI prolonged DA clearance from extracellular space. In conclusion, our findings provide the first evidence that phosphorylation of Thr53 in DAT protein is required for KOR mediated DAT upregulation in the central nervous system.

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Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.02/B17

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH Grant DA026947
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University of Florida Center for Addiction Research and Education (CARE)

Title: Dopamine transporter as a master regulator of functional connectivity and network topology of dopaminergic and GABAergic networks

Authors: *D. R. MILLER[1], D. T. GUENTHER[2], J. J. LEBOWITZ[1], A. J. REFOWICH[1], C. A. HANSEN[1], A. P. MAURER[2], H. KHOSHBOUEI[1];
[1]Neurosci., [2]Evelyn F. McKnight Brain Inst., Univ. of Florida, Gainesville, FL

Abstract: Dopamine neurotransmission plays a significant role in a plethora of behaviors from learning and memory, to motivation and addiction. Dopaminergic information is transmitted by consensus through synchrony (Beeler and Dreyer, 2019). The spatial temporal kinetics of dopamine signaling, comprising diffusion and synaptic transmission, are heavily regulated by dopamine transporter. Therefore, we hypothesized that perturbations in dopamine transporter activity will induce aberrant synchrony between dopaminergic neurons that alters the structure of local dopaminergic and GABAergic networks. To examine dopamine transporter regulation of GABAergic networks in the ventral midbrain regions, neurons were transduced with an AAV5 containing the genetically encoded calcium indicator GCaMP6f. Neuronal somas were segmented, and time resolved calcium signals were used as a proxy for neuronal activity. Networks were constructed by the top 15% strongest temporal functional connections at baseline (aCSF) before and after dopamine transporter activation through Spearman's rank correlation coefficient. In GABA networks, methamphetamine (a dopamine transporter activator) exposure produced a D2 receptor-sensitive network suppression and induction of subsets of strongly connected neurons to drop out from the network. Furthermore, methamphetamine altered the time course of network assortativity of GABA networks ($n = 71$ to 134 neurons, 6 independent experiments, one-way ANOVA with Tukey's post-hoc multiple comparisons, $p < 0.05$). To examine dopamine transporter regulation of dopaminergic networks, 200 μm coronal slices were prepared from the ventral midbrain comprising both the dopaminergic neuron rich regions substantia nigra pars compacta and ventral tegmental area of male and female mice. In both regions and sexes, dopamine transporter activation by methamphetamine increased the variance of functional connectivity that persisted even after blockade of GABA, glutamate and dopamine receptors signaling but sensitive to dopamine transporter blockade ($n = 5$ to 11 slices from 1-3 animals per group, one-way ANOVA with Tukey's post-hoc multiple comparisons, $p < 0.05$). Since this preparation is devoid of input from other brain regions, the induction of functional connectivity spikes is likely due to the intrinsic properties of dopaminergic neurons to self-organize their activity. Therefore, dopamine transporter is a fundamental regulator of dopaminergic synchrony, exhibiting cascading effects across both local dopaminergic and GABAergic networks. Our data reveal the central role of dopamine transporter activity in functional network modulation.

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Poster

461. Amino Acid Transport and Signaling

Location: Hall A

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Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

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UF CARE
UF IDP

Title: Dopamine transporter expressing peripheral immune cells are increased in drug naïve Parkinson's disease patients

Authors: *A. GOPINATH[1], P. MACKIE[1], L. SAADATPOUR[1], A. DOTY[2], A. RAMIREZ-ZAMORA[3], W. J. STREIT[1], M. S. OKUN[3], H. KHOSHBOUEI[1];
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Abstract: Introduction: Parkinson's disease (PD) is characterized by loss of substantia nigra (SN) dopaminergic neurons, resulting in reduced CNS dopamine transmission. PD is widely thought to start in the periphery; however, whether and how PD affects peripheral dopamine transmission remains unknown. Peripheral immune cells express key dopaminergic proteins, including dopamine transporter (DAT) and tyrosine hydroxylase (TH). Therefore, it is possible that the peripheral dopamine system is affected by PD pathology. Objective: We hypothesized that peripheral immune cells of PD patients exhibit dysregulated dopamine homeostasis. Methods/Results: Using flow cytometry we found human peripheral blood mononuclear cells (PBMCs) constitutively express DAT and TH with 90% of CD14+ cells expressing both markers. Upon examining PBMCs of PD patients receiving a variety of treatments, we found that DAT/TH positive PBMCs are elevated in PD patients compared to healthy controls (n=67 independent biological replicates, $P<0.05$) irrespective of the treatment modality applied. Importantly, in drug naïve patients diagnosed with PD we observed the highest increase in DAT/TH positive monocytes (n=5, $P<0.05$) compared to both treated PD patients and healthy individuals, suggesting observed changes correlate with disease pathology and not treatment interventions. Collectively, these data suggest a system-wide dysregulation of the dopamine system on peripheral immune cells in PD. To further understand the functional consequences of increased DAT+/TH+ PBMCs, we asked if DAT function was altered on PD monocyte-derived cells. Live cell fluorescence microscopy and biochemical analysis confirmed healthy human

monocyte-derived macrophages (MDM) express membrane-localized, canonically functional DAT (Km=3.2mM). Surprisingly, relative to healthy age-matched controls, PD patients' MDMs exhibited dramatically elevated DAT-mediated substrate uptake and increased membrane localization ($p<0.0001$, n=5 biological replicates). Conclusions: Taken together, these data are consistent with the interpretation that in PD peripheral dopamine homeostasis is dysregulated. Importantly, this presents PBMC DAT/TH as a potential biomarker for PD and suggests the peripheral dopamine system is functionally linked to the CNS dopamine system. Future work will aim to validate this biomarker and investigate the mechanistic connection between peripheral-CNS dopamine systems to elucidate the pathophysiological role of dysregulated monocyte dopamine transmission in PD.

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Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.04/B19

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: conacyt 220448
conacyt 167778

Title: Exposure to ambient fine and ultrafine particles alters dopaminergic transmission *in vitro*

Authors: *M. A. ANDRADE OLIVA[1], Y. DEBRAY-GARCIA[2,4], J. ESCAMILLA-SANCHEZ[1], R. GONZALEZ-PANTOJA[1], M. URIBE-RAMIREZ[3], A. DE VIZCAYA-RUIZ[3], J.-A. ARIAS-MONTANO[1];
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Abstract: Parkinson's disease, depression and schizophrenia have been associated with alterations in dopaminergic transmission and exposure to environmental pollutants, such as fine (FP < 2.5 μm) and ultrafine particles (UFP < 0.1 μm). The striatum is a neuronal nucleus with extensive dopaminergic afferents and a target of particle toxicity, which results in oxidative stress, inflammation, astrocyte activation and modifications in dopamine content and D_2 receptor (D_2R) density. In this work, FP or UFP were collected and characterized from the air of Mexico City. In striatal synaptosomes, exposure to FP and UFP inhibited [^{3}H]-dopamine uptake and increased depolarization-evoked [^{3}H]-dopamine. In membranes from rat striatum or CHO-K1 cells transfected with the long isoform of the human D_2R ($hD_{2L}R$), FP and UFP exposure increases D_2R affinity for dopamine, measure by displacement of [^{3}H]-spiperone binding. In

striatal slices and CHO-K1-hD_{2L}R cells, exposure to FP and UFP increased the potency of dopamine to inhibit forskolin-induced cAMP formation. The effects were more notorious by exposure to UFP than FP showing that factors such as size and composition could be involved. These results indicate that exposure to FP or UFP directly affect dopaminergic transmission.

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Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.05/B20

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: N.H. is supported by a fellowship by CRC815

Title: Projection-specific diversity of dopamine neurons within the medial substantia nigra

Authors: *N. HAMMER, S. STOJANOVIC, N. FARASSAT, J. ROEPER;
Goethe Univ. Frankfurt, Frankfurt, Germany

Abstract: Midbrain dopamine (DA) neurons are not only subdivided by their location within the midbrain, residing either in the ventral tegmental area (VTA) or the substantia nigra pars compacta (SNc), but also by their different axonal projection targets, e.g. the dorsomedial striatum (DMS), dorsolateral striatum (DLS), or distinct regions within the nucleus accumbens (NAcc) [1, 2]. DA neurons located in the medial SNc project either to DMS, DLS or the lateral shell of NAcc [2, 3]. These distinct projections of DA neurons are associated with distinct electrophysiological properties *in vitro* [1, 2]. Recently, we also identified significant *in vivo*differences between mSNc DA neurons projecting to the dorsal striatum (DMS/DLS) and lNAcc [3]: mSNc DA neurons projecting to lNAcc displayed more burst firing events per minute while they also possessed more pauses, longer periods of electrical silence. In contrast, mean in vivo frequencies and the coefficient of variations were not different between dorsal and ventral striatum projecting mSNc DA neurons [3]. When studying the different, retrogradely identified DA subpopulations within the mSN of adult C57Bl6 mice in more detail in vitro, we found that those DA neurons projecting to DMS showed the lowest intrinsic firing frequencies (DMS_{mSNc}= 1.6 ± 0.1 Hz, n = 27; $lNAcc_{mSNc}$ = 2.0 ± 1.7, n = 19; DLS= 2.5 ± 0.2 Hz, n = 20) and longest rebound delays (DMS_{mSNc}= 673.6 ± 82.1 ms, n = 24; $lNAcc_{mSNc}$= 426.8 ± 51.6 ms, n = 19; DLS_{mSNc}= 215.3 ± 37.6 ms, n = 20). As differences neuromodulatory control are expected to contribute to the *in vivo*activity of DA neurons in addition to their intrinsic excitability, we are currently investigating potential projection-specific differences in D2R-mediated inhibition of

mSNc DA neurons.
(1) Lammel et al., 2008, Neuron (2) Lerner et al., 2015, Neuron (3) Farassat et al., 2017, SFN 2017, 232.13/FF11

Disclosures: **N. Hammer:** None. **S. Stojanovic:** None. **N. Farassat:** None. **J. Roeper:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.06/B21

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: CRC 1193

Title: Distinct subthreshold activity of projection-specific dopamine neurons revealed by *in vivo* whole cell recording

Authors: *K. OTOMO[1,2], S. STOJANOVIC[1], N. FARASSAT[1], C. PALADINI[3], J. ROEPER[1]; [1]Inst. of Neurophysiol., Goethe Univ. Frankfurt, Frankfurt, Germany; [2]Intl. Max Planck Res. Sch. for Neural Circuits, Max Planck Inst. for Brain Res., Frankfurt, Germany; [3]UTSA Neurosciences Inst., Univ. of Texas at San Antonio, San Antonio, TX

Abstract: Ventral tegmental area (VTA) dopamine (DA) neurons play critical roles in motivation and reward- or aversion-based learning, as well as drug addiction and schizophrenia, by encoding environmental information to reinforce behavior. In the past decade, an increasing number of studies have demonstrated the heterogeneity of the midbrain DA neurons. Upon presentation of a rewarding or aversive stimulus, DA neurons can either be excited or inhibited depending on the subpopulation, which is associated with distinct axonal projection targets. In order to better understand DA subtype-specific computations, direct analysis of *in vivo* subthreshold properties of VTA DA subpopulations will be mandatory. As a first step, we recorded subthreshold activity from midbrain DA neurons in intact brains with the whole-cell configuration, using our recently-developed deep brain *in vivo* patch-clamp technique. Of the 132 putative DA neurons recorded with internal solution containing neurobiotin, 74 were successfully recovered and demonstrated to be dopaminergic, i.e., immuno-positive for tyrosine hydroxylase. These identified DA neurons displayed large variations in sag amplitudes during an injection of hyperpolarizing current, as well as differences in post-inhibition rebound behavior, ranging from transient rebound bursting to long pausing, resembling our previously published *in vitro* data. Additionally, our burst-triggered average analysis revealed two distinct subthreshold pre-burst signatures; one that directly entered a burst mode from the baseline membrane potentials, and another where the burst onset was preceded by a strong hyperpolarization. To define subthreshold behavior in distinct projection-defined VTA DA subpopulations, we are

currently evaluating different methods to record from projection-identified DA neurons, by combining *in vivo* patch clamp recordings either with highly-diluted fluorogold-mediated retrograde tracing or with GFP plasmid labeling.

Disclosures: K. Otomo: None. **S. Stojanovic:** None. **N. Farassat:** None. **C. Paladini:** None. **J. Roeper:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.07/B22

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH R01 DA041705

Title: Modeling the role of T-type calcium channels and their functional coupling to SK channels in projection-specific rebound properties of nigral dopamine neurons

Authors: *C. J. KNOWLTON[1], S. STOJANOVICH[2], J. ROEPER[2], C. C. CANAVIER[1]; [1]Cell Biol. and Anat., Louisiana State Univ. Hlth. Sci. Ctr., New Orleans, LA; [2]Inst. of Neurophysiol., Frankfurt am Main, Germany

Abstract: The electrical activity of midbrain dopamine (DA) neurons was long thought to homogeneously signal reward prediction errors. However, distinctions between DA subpopulations are now becoming increasingly clear; DA neurons might also provide start/stop signals for actions and signal salient and even aversive events. A morphologically realistic, multi-compartmental model calibrated by projection-specific *in vitro* electrophysiology data of DA neurons (see abstract by Stojanovic et al.) was used to propose mechanisms for axonal projection-specific responses of dopamine neurons in the substantia nigra (SN) during a prolonged hyperpolarization and the subsequent rebound phase. The model predicts that the degree to which the T-Type (CaV3) Ca^{2+} channels are de-inactivated controls whether DA SN neurons projecting to the dorsolateral striatum (DLS) exhibit a short latency rebound spike or longer latencies due to the presence of a subthreshold oscillation. Deeper hyperpolarizations favor the latter, because the larger Ca^{2+} influx activates SK channels sufficiently to prevent an action potential on at least one cycle of a subthreshold oscillation. Setting the SK or T-type conductance to zero eliminated subthreshold oscillatory responses and produced substantial transient increases in rebound spike frequency, consistent with experimental observations using SK and T-Type channel selective pharmacology. Another important result was that simply increasing conductance density of A-type (Kv4.3) K+ channels in the model eliminated both the fast rebound responses and the subthreshold oscillation; instead, the model produced only delayed post-inhibitory responses associated with a continuum of ramp-like subthreshold

responses consistent with observations in DMS-projecting DA neurons. Increased A-type conductance in DMS is shown to be consistent with more ramp-like interspike intervals in DMS projecting cells, deeper after-hyperpolarizations and a lower basal frequency relative to DLS projecting cells. Setting the SK conductance to zero in both simulated DLS and DMS projecting cells elicited rebound bursts mediated by the H current in the model. In the model, sustained rhythmic bursting could be obtained with SK block, an elevated L-type calcium conductance and a slowly activating Ca^{2+}-independent potassium current to repolarize the bursts. Distinct rebound properties and spike latencies after hyperpolarizing firing pauses are present between different DA projections and well captured by computer modeling implementing both realistic channel biophysics and calcium dynamics that control functional coupling.

Disclosures: C.J. Knowlton: None. **S. Stojanovich:** None. **J. Roeper:** None. **C.C. Canavier:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.08/B23

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH grant R01 DA041705 to JR

Title: T-type calcium channels mediate fast rebound bursting in dorsolateral striatum projecting dopamine neurons in the lateral substantia nigra

Authors: *S. STOJANOVIC[1,2], K. OTOMO[1], C. J. KNOWLTON[3], J. SHIN[1], C. C. CANAVIER[3], S. LAMMEL[2], J. ROEPER[1];
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Abstract: T-type calcium channels (LVA) are prominent in substantia nigra (SN) dopaminergic (DA) neurons, but their functional roles are not entirely understood. Previous studies have shown that LVA are being recruited through dopamine D2-receptor inhibition (Evans et al., 2017) and are involved in activation of SK potassium channels (Wolfart et al., 2002). To study the biophysical properties of LVA in DA SN neurons, we conducted comprehensive measurements of their biophysical properties *in vitro* in acute brain slices using patch-clamp recordings. This revealed a functional gradient throughout the medio-lateral axis of the SN, where lateral SN DA neurons showed a significantly greater LVA current amplitudes in comparison to those in medial SN DA neurons. In our next set of experiments, we retrogradely traced dorso-lateral striatum (DLS), as lateral SN preferentially projects to this striatal region (Lerner et al., 2015; Farassat et

al., unpublished), and compared it with other projection-specified DA subpopulations. After a hyperpolarizing current injection, DLS-projecting lateral SN DA neurons displayed strikingly faster rebound excitation, quantified as shorter latencies to the first spike and subthreshold oscillations, that were not observed in other DA subpopulations projecting to dorsomedial or ventral striatum. Selective pharmacological inhibition of LVA decreased rebound excitability and abolished the oscillations. In addition, application of SK-channel blockers led to high-frequency rebound bursting with shortened rebound delays. We are currently modelling the calcium dynamics of the flexible coupling between LVA and SK channels. Finally, *in vivo* patch-clamp whole-cell recordings of lateral SN DA neurons confirmed that the high rebound excitability is also present in the intact brain. We currently aim to identify synaptic inputs that might recruit this neuronal behavior in lateral SN DA neurons.

Disclosures: S. Stojanovic: None. **K. Otomo:** None. **C.J. Knowlton:** None. **J. Shin:** None. **C.C. Canavier:** None. **S. Lammel:** None. **J. Roeper:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.09/B24

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: Sigrid Juselius Foundation

Title: Social interactions are dependent on Ntrk2 signaling in the dopaminergic neurons

Authors: *M. SAHU[1], Y. PAZOS-BOUBETTA[1], M. PALMISANO[1], V. VOIKAR[1,2], E. CASTREN[1];
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Abstract: Dopamine in the vertebrate brain executes its functions via two prominent pathways; the nigrostriatal and the mesocorticolimbic pathway. The dopaminergic nigrostriatal pathway is essential for the control of voluntary motor behavior, while the mesocorticolimbic pathway is involved in controlling emotion-based behavior such as motivation and reward. Neurotrophin, brain derived neurotrophic factor (BDNF) signals through its high affinity receptor tyrosine kinase B (Ntrk2/TrkB). Both BDNF and Ntrk2 are widely expressed in the mid-brain dopaminergic neurons. BDNF can facilitate stress and drug induced neuro-adaptaion in the mesocorticolimbic pathway. Common pathological changes due to insufficient trophic support of BDNF via Ntrk2 on dopamine systems have been linked to psychosis, schizophrenia, attention deficit/hyperactivity disorder (ADHD), depression and addiction. Furthermore, antidepressants activate BDNF/Ntrk2 signaling and are concomitantly linked with increased dopamine levels in

the brain. Most of the studies have focused on region specific deletion of Ntrk2 from the dopaminergic subset of neurons. Previous studies have found BDNF signaling is highly crucial in the mesolimbic pathway during periods of chronic stress (Wook Koo et al 2016) but in the nigrostriatal pathway Nrtk2 deletion had no effect on neurodegeneration (Kramer et al 2007). This study investigates function of Ntrk2 in the dopaminergic neurons using a DAT-icre (Parlato et al 2006) mediated conditional knockout mouse. We used a tDtomato reporter to confirm the DAT expression patterns. These transgenic animals survive until adulthood without any morphological deformities. However, they are overweight compared to the control littermates and are innately aggressive. Absence of the Ntrk2 signaling hinders social recognition in three compartment sociability tests. These animals show memory impairment in novel object recognition task. Interestingly, the general motor behavior was found to be unaltered. Thus, Ntrk2 signaling is highly crucial in the mesocorticostriatal dopamine pathway. Further investigations on the reward circuitry and dopamine neuron development in these mice would dissect the potential target regions of Ntrk2 in the dopamine neurotransmission.

Disclosures: M. Sahu: None. **Y. Pazos-Boubetta:** None. **M. Palmisano:** None. **V. Voikar:** None. **E. Castren:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.10/B25

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH Grant DA026947
NIH Grant NS071122
NIH Grant OD020026
NIH Grant DA026947S1
NIH Grant DA042895
UF CARE

Title: Aging increases microglia senescence in the midbrain

Authors: *L. PHAN, F. SHAERZADEH, J. LEBOWITZ, M. DACQUEL, A. BECHTLE, W. HACHMEISTER, D. R. MILLER, W. J. STREIT, T. C. FOSTER, A. KUMAR, H. KHOSHBOUEI;
Neurosci., Univ. of Florida, Gainesville, FL

Abstract: Microglia are responsible for maintaining tissue homeostasis, neuronal support and protection. Since aging is the major risk factor for neurodegenerative diseases, including Parkinson’s disease, we hypothesized that the ratio of microglia to dopaminergic neurons as well

as microglial heterogeneity change with aging in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA). To address this hypothesis, we conducted stereological analyses to measure age-dependent changes in the number of microglia and dopaminergic neurons in the SNc and VTA of 1-, 6-, 9-, 18- and 24- month- old C57BL/J6 male mice. For quantification of the anatomical features of microglia, we stained coronal sections of the midbrain with tyrosine hydroxylase (TH) and Iba1, and performed stereological image analysis. In both brain regions, microglia increased in aged mice, whereas the number of TH+ cells reached a plateau after 1 month. Quantitative morphometry analyses revealed microglial complexity and projection area declined with aging while cell body size increased. Surprisingly, the contact sites between microglia and dopaminergic neurons in both regions increased in aged mice, suggesting an aging-dependent increase in microglial support of dopamine neurons. Furthermore, to assess for gait deficits with aging, ventral plane imaging (DigiGait) was utilized. Gait analysis indicates aging-dependent changes in mice gait indices. In conclusion, increases in microglial cell number, ratio of microglia to dopamine neurons, and physical contact sites suggest these innate biological mechanisms may compensate for the aging-dependent decline of microglia complexity (senescence) for continued neuronal support in aging within the SNc and VTA.

Disclosures: **L. Phan:** None. **F. Shaerzadeh:** None. **J. Lebowitz:** None. **M. Dacquel:** None. **A. Bechtle:** None. **W. Hachmeister:** None. **D.R. Miller:** None. **W.J. Streit:** None. **T.C. Foster:** None. **A. Kumar:** None. **H. Khoshbouei:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.11/B26

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: The Swedish Brain Foundation
Swedish Research Council
Systembolaget

Title: Involvement of astrocytes and volume regulated anion channels (VRACs) in the ethanol-induced increase of nucleus accumbens taurine in rats

Authors: *L. ULENIUS[1], K. ADEMAR[1], A. ANDRÉN[1], R. STOMBERG[1], L. ADERMARK[1], B. SÖDERPALM[1,2], M. ERICSON[1];
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Abstract: The harmful use of alcohol constitutes one of the leading factors for the total burden of disease and injury. Regarding the dopamine (DA) elevating properties of the drug, alcohol's

primary site of action appears to be within the nucleus accumbens (nAc), a central area of the mesolimbic dopamine system. We have previously shown that in order for ethanol to increase nAc DA levels, a simultaneous increase in endogenous taurine is required. The endogenous amino acid taurine exert a number of effects, including osmoregulation, and we hypothesize that taurine is released following ethanol exposure in order to re-equilibrate the osmotic pressure. Supporting this theory we have previously shown that inhibition of cell swelling, or manipulation of extracellular osmolarity, antagonizes ethanol-induced taurine and DA release in the nAc. The aim of the present study was to identify whether the ethanol-induced taurine increase originates from neurons or astrocytes and if the release is mediated via volume regulated anion channels (VRACs). Adult male Wistar rats were equipped with a microdialysis probe in the nAc and received acute treatment with the Na+ channel blocker tetradotoxin (TTX), the glial metabolic inactivator fluorocitrate or the VRAC inhibitor DCPIB alone, and together with ethanol (2.5 g/kg, i.p. or 300 mM locally perfused in the nAc) or vehicle. In all experiments extracellular levels of taurine and DA were examined in the dialysate every 20 minutes using HPLC. We found the ethanol-induced elevation of taurine to occur independently of TTX-administration, whereas the DA release was substantially decreased. Metabolic inactivation of astrocytes by fluorocitrate suppresses both the ethanol-induced increase in taurine, as well as the increase in DA. Furthermore, local perfusion with DCPIB attenuates ethanol-induced taurine release and prevents ethanol from increasing DA. We conclude that the ethanol-induced elevation of extracellular taurine in the nAc derives mainly from astrocytes and that taurine is likely released via VRACs. This strengthens the hypothesis that taurine acts as an osmotic regulator to antagonize ethanol-induced swelling of astrocytes.

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Poster

461. Amino Acid Transport and Signaling

Location: Hall A

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Program #/Poster #: 461.12/B27

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: CNPq
FAPERJ
CAPES

Title: Single cocaine exposure inhibits GABA uptake via dopamine D1-like receptors in frontal cortex in adolescent mice

Authors: R. C. KUBRUSLY[1], P. PANDOLFO[2], R. S. MARTINS[1], L. SOUZA[2], M. P. CARVALHO[1], V. P. MARTINS[1], M. SATHLER[3], ***D. FERREIRA**[4], M. D. PEREIRA[6], N. R.

PECCINALLI[1], R. A. REIS[7], G. D. FERREIRA[5], A. C. MANHAES[8];
[1]Dept. of Physiol. and Pharmacol., [2]Inst. of Biol., Fluminense Federal Univ., Niteroi, Brazil; [3]Colorado State Univ., Fort Collins, CO; [5]Inst. of Med. Biochem. Leopoldo de Meis, [4]Federal Univ. of Rio De Janeiro, Rio de Janeiro, Brazil; [6]Univ. of Sao Paulo, Ribeirao Preto, Brazil; [7]Inst. of Biophysics Carlos Chagas Filho, Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [8]Rio de Janeiro State Univ., Rio de Janeiro, Brazil

Abstract: Cocaine (COC) is a main psychostimulant that acts by increasing catecholaminergic neurotransmission mainly due to its effects on dopamine transporter (DAT). However, other transmitter systems may also be regulated by COC, including GABAergic circuits. Since the role of COC in modulating GABA reuptake is not defined, we investigated the molecular mechanisms related to the increase in GABA uptake induced by acute cocaine exposure and its effects on locomotor activity in adolescent mice. Behavioral experiments showed that COC increased locomotor activity and its effects were prevented by a previous treatment with SCH23390. A single COC exposure reduced both GABA uptake and GAT-1 protein levels. On the other hand, cAMP levels were increased after COC challenge. The major changes induced by acute COC on neurochemical assays and behavioral tests were avoided by blocking dopamine D1-like receptors. Our findings suggest that dopamine D1-like receptors are key players in the regulation of extracellular GABA levels through a single COC exposure in adolescent mice.

Disclosures: R.C. Kubrusly: None. **P. Pandolfo:** None. **R.S. Martins:** None. **L. Souza:** None. **M.P. Carvalho:** None. **V.P. Martins:** None. **M. Sathler:** None. **D. Ferreira:** None. **M.D. Pereira:** None. **N.R. Peccinalli:** None. **R.A. Reis:** None. **G.D. Ferreira:** None. **A.C. Manhaes:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.13/B28

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: DA026947
NS071122
OD020026
DA026947S1
DA043895

Title: Repeated methamphetamine exposure alters the baseline firing activity of ventral tegmental area dopamine neurons

Authors: *D. O. SAMBO[1], M. LIN[1], J. LEBOWITZ[1], D. MILLER[1], H. KHOSHBOUEI[2]; [2]Box 100244, [1]Univ. of Florida, Gainesville, FL

Abstract: Repeated exposure to low to moderate doses of methamphetamine have been shown to induce behavioral sensitization, including increased locomotor responses to the same dose of drug. While the exact mechanism of methamphetamine-induced behavioral sensitization is less clear, increased sensitivity of dopaminergic signaling including decreased activity of inhibitory D_2 autoreceptors (D_2R) is one proposed mechanism. We and other have shown acutely administered methamphetamine increases the frequency of firing activity of dopamine neurons and stimulates dopamine efflux via the dopamine transporter. Increased extracellular dopamine in the ventral tegmental area (VTA) in turn activates the inhibitory D_2Rs resulting in feedback inhibition and decreased activity of dopamine neurons. In this study, we investigated the effect of repeated methamphetamine exposure (2mg/kg/7days) on the baseline activity of VTA dopamine neurons. Whole-cell slice recordings in VTA dopamine neurons of methamphetamine vs. saline treated mice revealed that sub-chronic, systemic exposure to methamphetamine increased the *baseline* excitability of VTA dopamine neurons, such that methamphetamine-treated animals showed a more depolarized membrane potential and increased spontaneous firing activity. To our surprise, the "sag" current, as measured by the I_h-mediated current after application of hyperpolarizing current pulses, showed no change of methamphetamine vs. saline treated animals, suggesting no changes in the inhibitory function of the neurons. Analysis of current-evoked single action potential (AP) properties revealed that sub-chronic methamphetamine exposure narrowed the AP width, increased the AP amplitude, and decreased the depolarization input resistance. Further analysis revealed that these changes in basal neuronal activity were coupled to increased activity of Ca^{2+} channel activity as well as the frequency and amplitude of intracellular Ca^{2+} transients in VTA dopamine neurons. These findings suggest that in the absence of D_2R activation by high levels of dopamine, sub-chronic exposure methamphetamine exposure also alters the intrinsic, baseline firing activity of dopamine neurons in a Ca^{2+}-dependent manner.

Disclosures: D.O. Sambo: None. **M. Lin:** None. **J. Lebowitz:** None. **D. Miller:** None. **H. Khoshbouei:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.14/B29

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Title: Sensitive UHPLC analysis of GABA, glutamate, histamine and other amino acids for *in-vivo* microdialysis studies

Authors: *L. M. VAN HEERWAARDEN, H.-J. BROUWER, N. REINHOUD, M. EYSBERG;
Antec Scientific, Zoeterwoude, Netherlands

Abstract: Ultra-High Performance Liquid Chromatography (UHPLC) is a rapidly growing separation technique based on the application of LC columns with sub-2 µm particles operating at higher linear velocities and high back pressures. UHPLC offers advantages in chromatographic resolution, analysis speed, and sensitivity over conventional HPLC systems. The combination of Electrochemical Detection (ECD) with UHPLC can be a powerful solution to increase the sample throughput and sensitivity of neurotransmitter analysis in microdialysates, brain homogenates and other sample matrices. The versatile UHPLC ALEXYS Neurotransmitter Analyzer based on the DECADE Elite detector with SenCell is based on a flexible and scalable approach to offer an analysis solution for various neurotransmitter applications (biogenic amines and acidic metabolites, amino acid neurotransmitters and acetylcholine). A fast and sensitive method is presented for the analysis of the amino acid neurotransmitters GABA and Glutamate in microdialysates based on the new ALEXYS neurotransmitter analyzer (figure 1). Separation is achieved on a sub-2 µm particle column after automated pre-column derivatization with o-phthaldialdehyde (OPA). A step-gradient is used for clean-up of late eluting amino acid neurotransmitters present in microdialysate samples at the end of the run. With this approach excellent detection sensitivity can be achieved with minimal sample consumption. Other amino acids e.g. histamine, and large neutral nmino acids (LNAAs: Tyr, Val, Met, Orn, Leu, Ile, Phe, Lys, Trp) can be analyzed too using this method.
Method features:
• Automated odorless in-needle OPA-sulphite derivatization.
• Small sample use per analysis: 5 uL only (injection volume 1.5 µL)
• Fast and efficient separation using sub-2 µm particle column
• Post separation step-gradient to eliminate late eluting components
With this approach, a high sample throughput and low detection limit of around 10 nmol/L (15 fmol, 6 pg on column) for GABA is achievable.

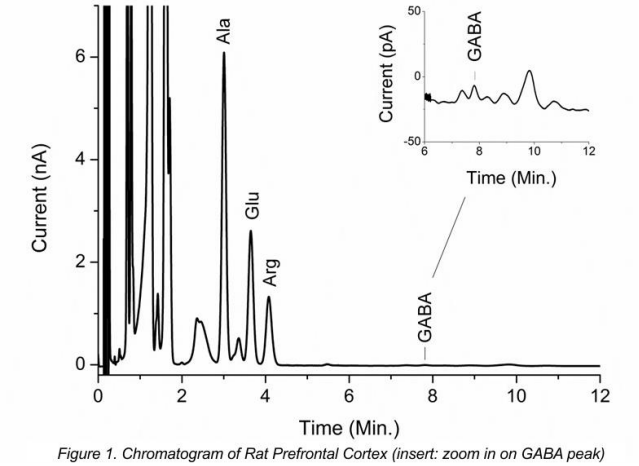

Figure 1. Chromatogram of Rat Prefrontal Cortex (insert: zoom in on GABA peak)

Disclosures: L.M. van Heerwaarden: None. **H. Brouwer:** None. **N. Reinhoud:** None. **M. Eysberg:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.15/B30

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH Grant MH112731

Title: Glycogen synthase kinase-3ß regulates the serotonin transporter function and trafficking in a phosphorylation-dependent manner

Authors: *D. RAGU VARMAN, L. D. JAYANTHI, S. RAMAMOORTHY;
Pharmacol. and Toxicology, Virginia Commonwealth Univ., Richmond, VA

Abstract: The serotonin (5-HT) transporter (SERT) plays a critical role in the regulation of serotonergic transmission in the central nervous system. While increasing evidence has shown that several protein kinases act as modulators in SERT regulation, the precise molecular mechanisms are mostly incomplete. In this study, the molecular mechanisms of glycogen synthase kinase-3ß (GSK3ß)-mediated SERT regulation and the site of transporter phosphorylation were investigated. We found that GSK3α/ß inhibitor CHIR99021 produced a time and dose-dependent elevation of SERT function with a concomitant increase in the SERT Vmax and surface expression. Moreover, while genetic interference of GSK3α/ß increased SERT function, coexpression of constitutively active GSK3ß-S9A decreased SERT function. The site-specific mutagenesis study revealed that mutation of serine 48 to alanine in SERT (SERT-S48A) not only completely abolished CHIR99021-mediated stimulation of 5-HT transport, but also the inhibitory effect caused by the active GSK3ß-S9A. Coexpression of GSK3ß-S9A with wild-type SERT reduced 5-HT transport, Vmax, and the surface SERT levels while enhancing SERT phosphorylation. However, coexpression of active GSK3ß-S9A with SERT-S48A did not change 5-HT transport, Vmax, surface SERT expression or SERT phosphorylation. Unlike wild-type SERT, SERT-S48A mutant did not exhibit functional stimulation following siRNA silencing of GSK3α/ß. Furthermore, Akt inhibitor AktX was effective in inhibiting both wild-type SERT and SERT-S48A mutant suggesting that GSK3 ß regulates SERT independent of Akt activation. Collectively, these findings are the first to reveal Ser-48 in SERT as a GSK3ß-dependent phosphorylation site, and that this site is required for GSK3ß-mediated SERT functional regulation.

Disclosures: D. Ragu Varman: None. **L.D. Jayanthi:** None. **S. Ramamoorthy:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.16/B31

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH Grant DA039451

Title: Neurokinin 1 and noradrenergic interplay in stress-mediated affective disorders and psychostimulant abuse: Studies from amphetamine-insensitive norepinephrine transporter mutant mouse model

Authors: *L. D. JAYANTHI[1], J. J. WINDLE[2], P. MANNANGATTI[1], S. RAMAMOORTHY[1]; [1]pharmacology and Toxicology, [2]Human and Mol. Genet., Virginia Commonwealth Univ., Richmond, VA

Abstract: Altered noradrenergic transmission and presynaptic norepinephrine (NE) transporter (NET) expression have long been associated with depression and drug addiction. Stress-related neuropeptides, including substance P, play an important role in drug abuse and relapse to drug-taking behavior. We have shown that neurokinin-1 receptor (NK1R) activation by substance P downregulates NET via PKC phosphorylation of the T258/S259 motif and that the same motif is required for AMPH-mediated NET downregulation (PMID:16740633; PMC3789959, PMC2939970). Our more recent studies show that AMPH-induced NET regulation and behavior are sensitive to NK1R antagonists and to manipulations targeting the NET-T258/S259 motif (PMC5266628; PMC5714664). To identify the neurobiological consequences of T258/S259-dependent in-vivo NET regulation, we have developed a prototypical mutant mouse model where the T258/S259 motif in the NET is replaced with an A258/A259 motif. Preliminary studies on the NET-T258A/S259A knock-in mice showed reduced NET functional expression in brain regions implicated in stress- and psychostimulant- mediated behaviors. Compared to WT males, NET-T258A/S259A males exhibit more anxiety-like behavior while such genotype-specific difference was not observed in the females. Compared to respective sexes of WT mice, male and female NET-T258A/S259A mice exhibit similar levels of basal locomotor activity. However, while AMPH-induced locomotor activation was similar in female T258A/S259A and WT mice, it was significantly reduced in male NET-T258A/S259A mice compared to WT males. AMPH-induced CPP was intact in both male and female T258A/S259A mice compared to WT male and females. While NK1R antagonist aprepitant attenuated AMPH-induced CPP in both sexes of WT and in T258A/S259A males, it failed to attenuate AMPH-induced CPP in T258A/S259A females. The data from T258A/S259A mice suggest that T258/S259-dependentNET regulation contributes to affective disorders and AMPH reward via NE-NK1 interplay. Thus, by expanding our appreciation of NK1R-mediated molecular events in AMPH-

mediated NET regulation, further studies on T258A/S259A mice will be extremely important and impactful in understanding NET regulatory mechanisms that are usurped by AMPH in the context of NE-NK1 interplay.

Disclosures: L.D. Jayanthi: None. **J.J. Windle:** None. **S. Ramamoorthy:** None. **P. Mannangatti:** None.

Poster

461. Amino Acid Transport and Signaling

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Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: MOST Grant 105-2320-B-002-055-MY3

Title: Role of inhibitory interneuron in the locus coeruleus in startle and pre-pulse inhibition behavior in mouse

Authors: *H.-C. TSAI[1], M.-Y. MIN[1], C.-C. KUO[1], H.-J. YAU[1], H.-W. YANG[2];
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Abstract: The locus coeruleus (LC) consists of noradrenergic (NA) neurons that have global axonal projection to the forebrain. LC-NA neurons exhibit two activation patterns, tonic and phasic. Tonic LC activation is correlated to the transition of wakefulness and alertness. In contrast, phasic LC activation is responding to changes in environmental contingencies and is able to modulate cognitive processes on a trial-by-trial basis. Nevertheless, the cell mechanism underlying the regulation of phasic and tonic LC activation remains largely unknown. The pre-pulse inhibition (PPI) is a commonly used operational measurement of sensorimotor gating, a fundamental and preattentive form of information-processing allowing organisms to filter information from external and internal domains. Previous study has shown that pharmacological activation of tonic LC activity decreased PPI. In this study, we reported an enhancement of PPI by suppression of local inhibitory interneurons in the LC with designer-receptor- exclusively-activated-by-designer-drug (DREADD). Male vesicular GABA transporter (VGAT)-Cre knock-in mice aged 5 weeks were injected with 20 nl adeno-associated virus (AAV) carrying a double-floxed inverted open reading frame hM4Di-mCherry into the LC. After 3 weeks of infection, we found that intraperitoneal administration of 1mg/kg of clozapine-N- oxide (CNO) to the mice 30 minutes before behavior test significantly increased PPI (PPI = 57.06 ± 3.22%, n=26), compared to those administered with vehicle (PPI = 42.14 ± 3.78%, n=26; p=0.0842556364685233, pair t test). On the contrary, the effect on PPI of CNO was neither observed in mice receiving the AAV injected to other pontine areas (n=9) nor in mice receiving control AAV injected into the LC (n=13). Besides, the unconditioned exploratory behaviors were unaltered in mice showing

increased PPI (n=14); linear regression analysis showed no significant relation between startle response and PPI. The results demonstrate that the mice showed more attentive possibly due to the enhanced phasic activation when local inhibitory interneurons in the LC were suppressed.

Disclosures: H. Tsai: None. **M. Min:** None. **C. Kuo:** None. **H. Yau:** None. **H. Yang:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.18/B33

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: Bloomsburg University Professional Experience Grant to Morgan Ilgenfritz
Bloomsburg University Professional Experience Grant to Dhir Gala
Donald D. Rabb Research Award from Department of Biological and Allied Health Sciences to Kathryn Sherry

Title: Investigating the localization and functional role of GABA receptors at neuromuscular synapses of the earthworm Lumbricus terrestris

Authors: M. J. ILGENFRITZ, K. M. SHERRY, D. N. GALA, ***W. L. COLEMAN**;
Biol. and Allied Hlth. Sci., Bloomsburg Univ. of Pennsylvania, Bloomsburg, PA

Abstract: The balance of excitatory and inhibitory signaling is critical for normal nervous system function, and is a key component of synaptic integration within the central nervous system. Synapses at the earthworm body wall muscle involve both excitatory and inhibitory components, which provides a useful model system for investigating these features. While a general inhibitory role of GABAergic signaling at the earthworm muscle has been established, the exact localization of the receptors and their individual functions are poorly understood. This study confirmed the presence of both GABA-A and GABA-B receptors at the body wall synapses using immunohistochemistry and confocal microscopy. The receptors localized to the same synaptic structures that were co-labeled for the presynaptic protein synapsin I. The GABA receptors could be presynaptic, postsynaptic, or both. To test the possibility that GABAergic receptors have presynaptic function, we performed an exploratory experiment using synaptogreen C4 dye (also called FM1-43), which stains synaptic vesicles through compensatory endocytosis. Following anesthesia in 10% ethanol saline solution, earthworms were dissected and cleaned to expose the ventral nerve cord and body wall muscles. Tissue sections were then loaded with 5uM synaptogreen C4 dye in an elevated K+ solution for 10 minutes. The loading solution for the experimental group also contained 5uM GABA. Following rinses and treatment with 200uM ADVASEP-7 for five minutes to reduce background fluorescence, staining of synaptic structures was assessed using confocal microscopy. Average fluorescence intensity was

quantified using measurement tools in Zen Blue software. To ensure that any differences in intensity were due to the treatment, all images were acquired using the same laser power and detector gain voltage. The average fluorescence intensity was not significantly different between the two groups (p=0.68, two tailed paired t-test with equal variance, control n = 40 structures analyzed, from 5 microscopic fields, from two worms; GABA treatment n = 130 structures analyzed, from 27 microscopic fields, from three worms). Under the tested conditions activation of GABAergic receptors had no effect on the presynaptic loading of synaptogreen, which suggests that these receptors may only have postsynaptic function. Future experiments will be aimed at elucidating specific GABA receptor functions at these synapses using electrophysiological techniques.

Disclosures: W.L. Coleman: None. **D.N. Gala:** None. **K.M. Sherry:** None. **M.J. Ilgenfritz:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.19/B34

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Title: Modulation of anion channel gating by C-terminal domains in excitatory amino acid transporters

Authors: *E. G. NEUREITER[1], D. TORRES-SALAZAR[1], M. H. CHENG[2], A. M. KARA[1], A. D. GONZALEZ-SUAREZ[1], C. GLASSER[1], J. GARCIA-OLIVARES[1], I. BAHAR[2], S. G. AMARA[1];
[1]Natl. Inst. of Mental Hlth., NIH, Bethesda, MD; [2]Computat. and Systems Biol., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Glutamate is the major excitatory neurotransmitter in the brain. The Excitatory Amino Acid Transporters (EAATs) are responsible for clearing excess glutamate released at synapses through uptake; excess extracellular glutamate leads to excitotoxicity and cell death. EAATs couple the influx of a molecule of glutamate, 3 sodium ions, and one proton with the counter transport of one potassium ion. In addition, EAATs function as anion selective channels. Although recent studies have been instrumental in beginning to understand the structural elements involved, the precise mechanisms and the structural links between glutamate transport and anion channel function are not fully understood. This exploratory study combines molecular dynamics simulations and electrophysiological techniques to elucidate the relationship between anion channel gating and glutamate transport in EAATs. A large body of evidence has supported a role for C-terminal domains in the gating mechanism of voltage-dependent chloride channels. In EAATs specifically, several studies have implicated C-terminal residues in cellular

trafficking, localization, and functionality. We constructed a computational model of EAAT4 including the C-terminal region in order to examine this region's effects on anion channel gating. This model suggests potential interactions between charged residues in the C-terminus in EAAT4 and in transmembrane domain 3 (TM3). We tested this potential relationship using electrophysiological recordings in *Xenopus* oocytes expressing different point mutations in TM3 (K119D, R123D, and R127D) and the C-terminus (E523, E528, and E530) as well as different truncations in the C-terminus of EAAT4. Glutamate uptake was measured using radiolabeled glutamate in uptake assays on transfected cells and oocytes. Our results show that a full truncation of the C-terminus (Q521X) disrupts anion channel gating and significantly reduces glutamate transport, indicating that the C-terminal domain plays a critical role in modulating the structural coupling between substrate transport and anion channel opening. Mutations in both the C-terminus and TM3 result in altered anion permeability ratios and anion channel permeation. These data demonstrate that the interaction of the C-terminus and TM3 is required for gating the anion channel. Our results help elucidate the molecular determinants underlying the structural coupling between anion channel gating and substrate translocation in EAATs.

Disclosures: E.G. Neureiter: None. **D. Torres-Salazar:** None. **M.H. Cheng:** None. **A.M. Kara:** None. **A.D. Gonzalez-Suarez:** None. **C. Glasser:** None. **J. Garcia-Olivares:** None. **I. Bahar:** None. **S.G. Amara:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.20/B35

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: CIHR

Title: The effects of D-serine on tectal cell dendritic morphology and retinotopic map development

Authors: *Z. CHORGHAY[1], V. LI[1], A. SCHOHL[1], E. S. RUTHAZER[2];
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Abstract: The N-methyl-D-aspartate type glutamate receptor (NMDAR) is essential for precise neural circuit refinement during development, through its effects on arbour morphology, synaptic stability, and plasticity. Our lab previously demonstrated that the gliotransmitter D-serine, an endogenous co-agonist for NMDARs, promotes glutamatergic synapse maturation, and stabilizes axonal structural and functional inputs in the developing visual system of the Xenopus tadpole. In this model, retinal ganglion cells (RGC) from one eye send contralateral projections to the optic tectum, allowing us to parse out presynaptic (RGC axons) from postsynaptic (tectal

dendrites) effects. Here, we further investigate the role of D-serine in circuit refinement, focusing on the postsynaptic side, by examining its effects on tectal cell dendritic morphology and the retinotopic map. To study morphology, we co-electroporated Cre-dependent GFP and dilute Cre plasmids into the tectum to stochastically label recently-differentiated single cells. We performed in vivo two-photon imaging every 24 hours for 4 days to detect morphological changes in these cells, following rearing of tadpoles in D-serine versus control. To extract retinotopic maps, we microinjected RNA into one blastomere at the two-cell stage, expressing the genetically-encoded calcium sensor GCaMP6s in half the animal i.e. tectal cells in one hemisphere and contralaterally projecting RGC axons in the other. We presented these animals with monocular visual mapping stimuli while performing rapid 4D calcium imaging of the tectum, then correlated fluorescence intensity changes to the positions of visual stimuli. The consequences of NMDA receptor signal enhancement on map refinement were tested by comparing maps in tadpoles reared in D-serine versus control. We find that D-serine does not interfere with the emergence of coarse retinotopic maps, but does decrease the complexity of dendritic morphology and produce alterations in overall map organisation. Overall, these findings provide support for the potential role of D-serine in neural circuit refinement, through its action on NMDAR-mediated neurotransmission, which has been implicated in neural circuit development, plasticity, and visual processing.
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Disclosures: Z. Chorghay: None. **V. Li:** None. **A. Schohl:** None. **E.S. Ruthazer:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.21/B36

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: NIH R01NS051445
NIH R01 NS105767

Title: Cysteine transporter compensation occurs in the brains of system x_c^- null mice

Authors: H. SOSNOKSI, M. M. MORGAN, ***S. J. HEWETT**;
Syracuse Univ., Syracuse, NY

Abstract: To avoid excitotoxicity and oxidative stress, the concentration of extracellular glutamate in the brain must be tightly regulated and antioxidants, such as the tripeptide γ-glutamyl cysteinyl glycine [aka glutathione (GSH)], must be dynamically produced. Several transporters, including excitatory amino acid transporters (EAATs) and system x_c^-, work to maintain extracellular glutamate levels by balancing its uptake and release, respectively.

Additionally, system x_c^- is known to import cystine, an amino acid fundamental to the production and maintenance of cellular GSH. Yet, mice that are null for system x_c^- appear healthy and, in previous studies, we found their brains are protected from, rather than more vulnerable to, glutamate excitotoxicity and oxidative stress. These data indicate that system x_c^- null mice may employ alternative glutamate or cystine/cysteine transport mechanisms [e.g., Excitatory Amino Acid Transporters (EAATs) 1-3, the Alanine-Serine-Cysteine-Transporters (ASCTs) 1 or 2, and/or the Large Neutral Amino Acid Transporter (LAT) 2] to regulate glutamate and/or sustain GSH levels *in vivo.* Thus, the objective of this work was to determine whether loss of system x_c^- leads to compensatory changes in the aforementioned transporters in brain. Toward this end, we measured and compared the striatal, hippocampal and cortical plasma membrane protein levels of EAAT1, 2, and 3, ASCT-1 and LAT-2 between system x_c^- null and wild-type mice via Western Blot Analysis. Mouse null for system x_c^- showed a significant increase in EAAT1 and EAAT3 expression over levels measured in wild-type control brains in the striatum only. Expression of LAT-2 increased significantly in all three brain regions ─striatum, hippocampus and cortex ─ of the system x_c^- null mouse tested, whereas no change in either EAAT2 or ASCT1 was measured in any brain region as compared to wild-type control brain. Thus, compensatory changes in transporter expression occurs in brains of mice null for system x_c^- in both a transporter type and brain region specific manner.

Disclosures: H. Sosnoksi: None. **M.M. Morgan:** None. **S.J. Hewett:** None.

Poster

461. Amino Acid Transport and Signaling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 461.22/B37

Topic: B.01. Neurotransmitters/ Transporters/ and Signaling Molecules

Support: 1SC1MH086070-01

Title: Characterization of a putative *Drosophila melanogaster* glycine transporter, and its specificity towards different amino acids

Authors: *E. L. PADILLA[1], A. B. LOPEZ[3], F. FRATEV[2], S. SIRIMULLA[2], M. MIRANDA-ARANGO[1];
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Abstract: Glycine is a major inhibitory neurotransmitter in the vertebrate central nervous system where the extracellular levels are controlled by two glycine transporters (GlyT1 and GlyT2). GlyTs belong to the solute carrier 6 family that group secondary active transporters dependent of

sodium and chloride to transport their substrates. While glycine transporters are essential for survival in mammals, their homologues and expression patterns in invertebrates are features not known. By sequence homology, Stuart et al., 2006 identified the gene CG5549 in *Drosophila melanogaster* to have the highest sequence homology with the vertebrate glycine transporters and later, in a separate study Ceriani et al., 2017, confirm that the gene CG5549 (Dmel-GlyT2) can transport glycine. However, neither report provided evidence of the specificity and kinetic analysis. In this study, we subjected the CG5549 to homology modelling and docking using the atomic coordinates of close relatives, the serotonin and dopamine transporters. We obtained a 3D model of the transporter that show the possible binding cage for glycine and ion binding sites. Initial biochemical characterization suggest that CG5549 is a more general amino acid transporter with low affinity for glycine. Further analysis should elucidate the substrate specificity and kinetic properties of this transporter.

Disclosures: E.L. Padilla: None. **A.B. Lopez:** None. **F. Fratev:** None. **S. Sirimulla:** None. **M. Miranda-Arango:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.01/B38

Topic: B.04. Ion Channels

Support: SFB 1328/A07
FOR 2419/P07
SFB 1047/A03
TRR 166/A03

Title: Bidirectional control of neuronal activity using light-activated potassium channels

Authors: *O. M. CONSTANTIN[1], S. GAO[2], J. YU-STRZELCZYK[2], S. YANG[2], G. NAGEL[2], T. G. OERTNER[1], C. E. GEE[1];
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Abstract: Optogenetic stimulation of neurons is a powerful approach that allows light evoked depolarization and firing of neurons. The number of genetically encoded tools for neuronal excitation has greatly increased in the last years, whereas the toolbox available for reversibly silencing neuronal activity is limited. Considering the importance of K^+ for setting the membrane potential, light-activated K^+ channels would allow rapid inhibition of individual neurons or populations with little effect on other ion gradients. Here we present an improved version of a novel light-gated K^+ selective channel (Beck et al., Frontiers in Neuroscience 2018). The new

optogenetic tool is a tandem construct developed by fusing bPAC, a bacterial photo-activated adenylyl cyclase to a cyclic nucleotide-gated channel with high permeability for K^+. The high light sensitivity of bPAC and the channel's high K^+ permeability allow for strong hyperpolarization of the plasma membrane even with short pulses of low intensity light. Rat hippocampal neurons expressing the fusion construct are strongly hyperpolarized (~20 mV) when blue light is applied (50 ms, 470 nm, 1 mW/mm^2). This hyperpolarization completely blocked action potentials induced by up to 2 nA somatic current injections, an effect which lasted around 40 s. This blockade of firing could be easily extended to 5 minutes by repeatedly flashing blue light at 30 s intervals. The ability of bPAC to integrate light over time as well as its narrow activation spectrum allows for this new fusion construct to be used for dual color excitation-inhibition experiments. Using prolonged 400 nm light at extremely low intensity (0.001 mW/mm^2), action potentials generated by red-light activation of co-expressed Chrimsons were fully blocked without any cross-activation. By expressing both the fusion potassium channel and a Chrimson in presynaptic CA3 neurons, we could bi-directionally control synaptic transmission to postsynaptic CA1 neurons. The improved light-gated potassium channel is a new tool that expands the inhibitory optogenetic toolbox and allows for precise and potent manipulation of membrane potential and when combined with a Chrimson variant allows precise spiking or inhibition of presynaptic neurons with blue and red light.

Disclosures: O.M. Constantin: None. **S. Gao:** None. **S. Yang:** None. **G. Nagel:** None. **T.G. Oertner:** None. **C.E. Gee:** None. **J. Yu-Strzelczyk:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.02/B39

Topic: B.04. Ion Channels

Support: This study was supported by the SFB CRC-128 (B06 to Meuth/Budde/Pape)

Title: Altered excitability in a mouse model of multiple sclerosis: Role of voltage gated potassium channels

Authors: *L. FAZIO[1], M. CERINA[1], V. NARAYANAN[1], T. BUDDE[2], S. G. MEUTH[1]; [1]Neurol. Dept. with Inst. of Translational Neurol., [2]Inst. of Physiol. I, Univ. of Muenster, Muenster, Germany

Abstract: Multiple sclerosis (MS) is an inflammatory disease of the central nervous system, characterized by the appearance of randomly distributed brain lesions, involving both white and gray matter structures. These lesions are accompanied by episodes of de- and remyelination along with neuroaxonal degeneration. Recent findings pointed out that the early phase of

remyelination is characterized by a cortical hyperexcitability, suggesting an altered expression of certain ion channels along demyelinated neurons. Voltage-gated potassium channels (K_v) play a pivotal role in shaping neuronal excitability. The opening of these channels elicits and outward current repolarizing the cell and therefore, pharmacological targeting of these channels represents an appealing strategy for the treatment of various diseases. However, the role of these channels in autoimmune disorders still requires further investigations. To address this issue, we induced an experimental autoimmune encephalomyelitis in C57Bl6 mice, a widely used experimental model of MS. Furthermore, to mimic the appearance of lesions characteristic of MS, we focally injected a cocktail of the cytokines tumor necrosis factor alpha and interferon gamma in the primary auditory cortex. To investigate the contribution of K_v channels to cortical hyperexcitability, we electrophysiologically characterized cortical neurons in vitro. We therefore performed whole cell recordings on acute living brain slices from mice with a focal lesion and respective controls, at different stages of the disease. In current clamp, neurons from perilesional areas showed increased number of action potentials both in the acute (+100%) and late (+284%) phase of the disease in comparison to controls. However, specific K_v channel modulators were still efficient in limiting their excitability. In voltage clamp, measuring the outward current generated by these channels in the acute and late phase of the disease showed a reduced current amplitude (-40% and -41%, respectively) in accordance with an increased excitability. Taken together, our results suggest the involvement of K_v channels in generating and sustaining cortical hyperexcitability in our MS model and that the pharmacological modulation of K_v channels can partially rescue the normal phenotype.

Disclosures: **L. Fazio:** None. **M. Cerina:** None. **V. Narayanan:** None. **T. Budde:** None. **S.G. Meuth:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.03/B40

Topic: B.04. Ion Channels

Support: NNSFC 31270882
NBRP 2013CB531302

Title: Ion channel mechanism of phenylephrine induced spontaneous firing in DRN 5-HT neurons

Authors: *J. WANG[1], Y. WANG[2], X. DU[3], H. ZHANG[4];
[1]Dept. of Pharmacol., Shijiazhuang, China; [2]Hebei Med. Univ., Shijiazhuang, China; [4]Pharmacol., [3]Hebei Med. Univ., Hebei, China

Abstract: Abstract
Over the years accumulated evidence implicate serotonergic (5-HT) system originating in the dorsal raphe nucleus (DRN) in the pathogenesis and treatment of psychiatric disorders. The firing activity of DRN 5-HT neurons is the key determinant in controlling the serotonin transmission and the emotion-related behaviors. 5-HT neurons are not intrinsic pacemakers but rather depend on extrinsic inputs to drive their firing, mainly the noradrenergic input trigger from the locus coeruleus (LC). Accordingly, noradrenergic agonist, e.g. phenylephrine (PE) could induce spontaneous firing of 5-HT neurons in brain slices which otherwise are quiescent. However, it is not clear how exactly PE induces this spontaneous activity, although some ion channels, e.g. A-type potassium channels have been suggested to play a role. In this study, we attempted to study the ion channel mechanism of phenylephrine-induced spontaneous firing in DRN 5-HT neurons. We found that the A-type potassium channels, the calcium-activated small-conductance potassium channels (SK channels) and the M-type potassium channels are likely the targets of PE modulation which contribute to the PE-induced spontaneous activity of DRN 5-HT neurons.

Disclosures: **J. Wang:** None. **Y. Wang:** None. **X. Du:** None. **H. Zhang:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.04/B41

Topic: B.04. Ion Channels

Support: NSFC Grant 31671078

Title: Dopamine D2 receptor-mediated modulation of rat retinal ganglion cell excitability

Authors: ***N. YIN**, Y.-L. YANG, S. CHENG, H.-N. WANG, Y. MIAO, F. LI, Z. WANG; Inst. of Brain Science, State Key Lab. of Med. Neurobio. and MOE Frontiers Ctr. for Brain Science, Fudan Univ., Shanghai, China

Abstract: Retinal ganglion cells (RGCs) are output neurons in retinal circuity. Modulation of RGC excitability may affect the retinal visual information integration and processing. Here, whether and how dopamine D2 receptor modulate RGC excitability were explored in acutely isolated rat RGCs using whole-cell patch-clamp techniques. Extracellular application of quinpirole (10 μM), a selective D2 receptor agonist, significantly suppressed outward K^+ currents of the cells, which was reversed by sulpiride (10 μM), a selective D2 receptor antagonist. We further showed that quinpirole selectively suppressed glybenclamide- and 4-aminopyridine-sensitive K^+ current components, but had no effect on the tetraethylammonium-sensitive one. In addition, quinpirole significantly and selectively enhanced Nav1.6 voltage-

gated Na^+ currents. The effects of quinpirole on K^+ and Na^+ currents were mediated by intracellular cAMP/protein kinase A (PKA), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), and calcium/calmodulin-dependent protein kinase II (CaMK II) signaling pathways, but not by phospholipase C (PLC)/protein kinase C (PKC) signaling. Under the current-clamp conditions, extracellular application of quinpirole significantly increased the numbers of action potentials evoked by positive current injections in RGCs, suggestive of enhanced cell excitability. Our results indicate that D2 receptor activation increases rat RGC excitability by suppressing glybenclamide- and 4-aminopyridine-sensitive outward K^+ currents and enhancing Nav1.6 currents through the intracellular cAMP/PKA, CaMKII and MAPK/ERK signaling pathways.

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Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.05/B42

Topic: B.04. Ion Channels

Support: NS102239

Title: Interaction between HCN and slack channels regulates mPFC pyramidal cell excitability and working memory function

Authors: *L. EL-HASSAR[1,3], D. DATTA[2], M. CHATTERJEE[1], A. F. ARNSTEN[2], L. K. KACZMAREK[1];
[1]Pharmacol., [2]Neurosci., Yale Univ. Sch. of Med., New Haven, CT; [3]iBV, Univ. de Nice Sophia Antipolis, Nice, France

Abstract: Neuronal networks of the prefrontal cortex (PFC) subserve working memory (MW), the ability to retain short-term neuronal information in absence of sensory stimulation. This aspect of mental representation has been extensively studied in monkeys and rats using spatial working memory tasks and has been shown to depend on persistent firing of layer III dPFC pyramidal cells. Persistent firing of these neurons for a period of up to several seconds is therefore considered to be the cellular basis for spatial working memory. Disruption of dPFC pyramidal cell firing during stress or mental illness leads to working memory deficits and to inappropriate behavior. One mechanism by which stress can disrupt WM performance is through excessive release of catecholamines, which activate cAMP signaling to influence the activity of ion channels and alter PFC pyramidal cell firing. For example, increased open probability of hyperpolarization-activated cyclic nucleotide-gated (HCN) channels in response to elevated

cAMP during stress alters WM performance by decreasing firing rate. This finding raises the question of how activation of HCN channels, which normally produces depolarization and increased firing, reduces the firing of PFC pyramidal cells. We are testing the hypothesis that Na^+ influx through HCN channels activates Na^+-activated K^+ (K_{Na} or Slack) channels to hyperpolarize the membrane and raise spike threshold. Slack channels are highly expressed in the frontal cortex and human Slack mutations produce severe intellectual disability. We have tested interactions between HCN1 and K_{Na} channels in PFC pyramidal neurons using immunoelectron microscopy, co-immunoprecipitation, patch-clamp recordings and behavior. First, we found that ZD7288, a specific blocker of HCN channels reduces K_{Na} current in pyramidal cells but has no effect on Slack current in an HEK cell line stably expressing this K_{Na} channel, demonstrating that ZD7288 does not interact with Slack directly. Second, we found that Slack channels co-immunoprecipitate with HCN1, and, using immunoelectron microscopy, that HCN1 and Slack channels colocalize on the same dendritic spine of PFC pyramidal cells. Third, we have found that blockers of Slack channels (and of HCN1 channels) improve working memory performance and that the actions of Slack and HCN channel blockers occlude each other in the working memory test. Our ongoing results suggest that a common pathway between HCN and Slack channels exists to regulate the excitability of dPFC pyramidal neurons and WM performance

Disclosures: L. El-Hassar: None. **D. Datta:** None. **M. Chatterjee:** None. **A.F. Arnsten:** None. **L.K. Kaczmarek:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

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Topic: B.04. Ion Channels

Support: CNRS
University of Bordeaux
LabEx BRAIN ANR-10-LABX-43
DFG grant SFB1328-Z02

Title: Increased surface P2X4 receptor expression regulates synaptic plasticity and behavior in P2X4 internalization-defective knock-in mice

Authors: *K. S. PILCH[1], E. BERTIN[1], T. DELUC[1,3], A. MARTINEZ[1], J.-T. POUGNET[1], E. DOUDNIKOFF[1], A.-E. ALLAIN[2], P. BERGMANN[4], M. RUSSEAU[5], E. TOULMÉ[1], E. BEZARD[1], F. KOCH-NOLTE[4], P. SÉGUÉLA[3], S. LÉVI[5], B. BONTEMPI[1], F. GEORGES[1], S. S. BERTRAND[2], O. NICOLE[1], E. BOUÉ-GRABOT[1];
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Abstract: ATP signaling and surface P2X4 ATP-gated receptor channels are upregulated in various neurological disorders including chronic pain, epilepsy and neurodegenerative diseases such as Alzheimer's disease (AD) or amyotrophic lateral sclerosis (ALS). P2X4 displays a widespread distribution in CNS neurons and glial cells as well as in multiple peripheral cell types throughout the body. A key question regarding the role of purinergic signaling in health and disease is the function of this upregulated surface P2X4 state observed in specific cell types. To elucidate the cell-specific functions of P2X4 in a pathological context, we created a conditional transgenic knock-in P2X4 mouse line (floxed P2X4mCherryIN) allowing the Cre activity-dependent genetic swapping of the internalization motif of P2X4 by the fluorescent protein mCherry to prevent constitutive endocytosis of P2X4. We describe and characterize two distinct knock-in mouse lines expressing non-internalized P2X4mCherryIN either in excitatory forebrain neurons (CamK2) or in all cells natively expressing P2X4 (CMV). The genetic substitution of wild-type P2X4 by non-internalized P2X4mCherryIN in both knock-In mouse models does not alter the sparse distribution and subcellular localization of P2X4 but leads to a cell-specific increased surface P2X4 expression mimicking the pathological upregulated P2X4 state. Floxed, CamK2- and CMV-P2X4mCherryIN mice were viable, normal in size, reproduced normally and displayed no obvious physical or behavioral abnormalities. We provide evidence using a battery of behavioral tests that the increase in P2X4 at the surface of excitatory neurons decreases anxiety and impairs memory processing. In addition, we demonstrate that increased surface P2X4 expression blocks long-term potentiation (LTP) and alters LTD at hippocampal CA1 synapses. These effects are more pronounced when surface P2X4 expression is specifically increased in forebrain excitatory neurons. The key finding of this study is that the increased surface expression of P2X4 in forebrain excitatory neurons is a major regulator of hippocampal synaptic plasticity, learning and memory and anxiety functions. Overall, we provide an innovative knock-in P2X4 model to study the functional contributions of upregulated P2X4 in specific cells of the nervous system but also in peripheral tissues throughout the body.

Disclosures: K.S. Pilch: None. **E. Bertin:** None. **T. Deluc:** None. **A. Martinez:** None. **J. Pougnet:** None. **E. Doudnikoff:** None. **A. Allain:** None. **P. Bergmann:** None. **M. Russeau:** None. **E. Toulmé:** None. **E. Bezard:** None. **F. Koch-Nolte:** None. **P. Séguéla:** None. **S. Lévi:** None. **B. Bontempi:** None. **F. Georges:** None. **S.S. Bertrand:** None. **O. Nicole:** None. **E. Boué-Grabot:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.07/B44

Topic: B.04. Ion Channels

Support: CNRS
Université de Bordeaux

Title: Insulin regulates P2x4 receptor function and promotes its rapid delivery to the cell surface

Authors: E. BERTIN[1], A. MARTINEZ[1], A. R. ASE[2], E. EISELT[1], P. A. SEGUELA[2], M. EMERIT[3], *E. BOUE-GRABOT[1];
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Abstract: P2X receptors (P2X) are ATP-gated non-selective cation channels highly permeable to calcium widely expressed in many tissues. In the central nervous system (in neurons and glia), macrophages, epithelia tissues, vascular endothelial cells they participate in synaptic neuromodulation and neuroglial communication, inflammation, chronic pain or vascular tone. P2X4 are constitutively internalized by dynamin-dependent endocytosis and mainly retained intracellular in basal conditions. P2X4 have been shown to be upregulated at the surface of cells in various pathophysiological contexts such as ischemia, chronic neuropathic pain or neurodegenerative diseases, indicating the importance of the regulation of P2X4 function and trafficking. Insulin was previously shown to modulate the trafficking and function of GABA-A and AMPA receptors in CNS neurons. Here we show that insulin induces a rapid (2-min incubation) and long-lasting increase of the amplitude of ATP-evoked currents in *Xenopus* oocytes expressing mammalian P2X4 receptors. Insulin blocks also the rundown of P2X4 responses observed during repeated application of ATP. In contrast, no change in ATP responses from oocytes expressing P2X2 or P2X3 receptors is observed in the presence of insulin. Internalization-deficient P2X4 mutants (P2X4Y378A, P2X4FlagIN or P2X4mCherryIN) responses are potentiated in a similar manner by insulin. In addition, western blot analysis of surface biotinylated and total protein fractions from oocytes shows that insulin increases the number of surface wild-type and internalization-deficient P2X4 mutants. Furthermore, ATP-evoked P2X4 currents and surface number of native P2X4 are significantly increased by insulin in mouse microglia as well as in native peritoneal macrophages from wild-type or knockin P2X4mCherryIN mice. The insulin-mediated increase of surface and function of P2X4 is abolished in presence of tyrphostin or TeTN, two blockers of insulin receptors and exocytosis, respectively. By real-time imaging on live cortical neurons expressing P2X4-pHluorin123 or P2X4Y378A-pHluorin123, we show that application of insulin causes a rapid and strong increase in fluorescence intensity of both constructs revealing the increase of insertion of P2X4 at the surface. Altogether, these results show that insulin potentiates P2X4 receptors in various cell types (neurons, microglia and macrophages) very likely via delivery of new P2X4 channels to the surface.

Disclosures: E. Bertin: None. **A. Martinez:** None. **A.R. Ase:** None. **E. Eiselt:** None. **P.A. Seguela:** None. **M. Emerit:** None. **E. Boue-Grabot:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.08/B45

Topic: B.04. Ion Channels

Title: Identification of hyperforin binding site at TRPC6 channels

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Abstract: Depressive disorders are ranked on the second place of all known psychiatric diseases in humans and affect currently 300 million people of all ages worldwide according to the WHO. Extracts of St. John's wort plant (Hypericum perforatum) have turned out to be a clinical effective alternative to classical antidepressants to treat mild to moderate depression. The antidepressive active constituent of St. John's wort is the phloroglucinol hyperforin, which has been described as a potent uptake inhibitor of several neurotransmitters like serotonin, dopamine and norepinephrine and for the first time in 2007 as a selective activator of canonical transient receptor potential (TRPC) channel 6. However, the binding mode of Hyperforin to TRPC6 is still unknown. TRPC6 is a plasma membrane located nonselective cation channel permitting the uptake of mono- and divalent cations such as sodium and calcium. TRPC6 channels play an important role in neuronal Ca^{2+} signaling. Moreover, studies have already demonstrated that activation of TRPC6 channel via hyperforin regulate synaptic plasticity which is negatively changed in depression. Based on their amino acid sequences and functional similarities, the TRPC family can be divided into 4 groups: TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7. As previously mentioned, hyperforin is a selective activator of TRPC6, which shows no activation of the TRPC6 homologues TRPC3 and TRPC7, respectively. Therefore, we screened several TRPC6 mutants by exchanging amino acids in TRPC6, which differed from TRPC3 or TRPC7 to evaluate the binding site of hyperforin. Afterwards, we started to focus on a TRPC6 mutation which showed no activity towards hyperforin. To demonstrate that this amino acid sequence is responsible for hyperforin mediated TRPC6 activation and selectivity over TRPC3, we exchanged the corresponding amino acids in TRPC3 with the respective amino acids of TRPC6. In single cell Ca^{2+} imaging experiments and patch clamp experiments, hyperforin now also activates mutated TRPC3 channels. Taken together, we identified the putative binding site of hyperforin at TRPC6 channels.

Disclosures: Y. El Hamdaoui: None. **K. Friedland:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.09/B46

Topic: B.04. Ion Channels

Support: National Research Foundation of Korea (NRF) Grant 2019R1A2C2003616
National Research Foundation of Korea (NRF) Grant 2017R1A5A2015395

Title: TRPM2 regulates NPAS4 activity in the mouse hippocampal neurons

Authors: *S. KO[1,2], M. CHOI[1], H. SON[1,2];
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Abstract: Transient receptor potential melastatin type 2 (TRPM2) is an oxidative stress-sensing calcium-permeable channel that is abundantly expressed in the brain. TRPM2 signaling has been linked to several pathophysiological processes in the brain and proposed as a potential therapeutic target for neurological diseases. We previously demonstrated that *Trpm2* knockout mice had an antidepressant-like phenotype. Here we show that genetic ablation of TRPM2 increased phosphorylation of histone deacetylases 5 (HDAC5) and its nuclear export in mouse hippocampus. In addition, TRPM2 deficiency increased expression of neuronal PAS domain protein 4 (NPAS4), a neural activity-dependent transcriptional factor, which is negatively regulated by HDAC5. Conversely, H_2O_2-induced TRPM2 activation decreased NPAS4 expression in a dose-dependent manner in mouse hippocampal neuron. These results suggest that NPAS4-dependent gene expression might be altered in *Trpm2* knockout mice. We are currently investigating a role of NPAS4 in the antidepressant-like behavior of *Trpm2* knockout mice.

Disclosures: S. Ko: None. **M. Choi:** None. **H. Son:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.10/B47

Topic: B.04. Ion Channels

Support: FONDECYT 1181814

FONDECYT 11180536
USA1899-Vridei 021943LE-PAP Univesidad de Santiago de Chile

Title: Cholinergic receptors activate TRPM4 in pyramidal cortical neurons at mice mPFC layer 2/3

Authors: *E. LEIVA-SALCEDO, F. NAVARRO, F. A. PERALTA, D. RIQUELME;
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Abstract: Medial prefrontal cortex receives cholinergic inputs from basal forebrain and local inputs from interneurons in the layer 1 which shapes its electrical properties. This cholinergic modulation specifically targets different cortical layers, the neurons wherein express different cholinergic receptors, giving an increasing processing and control capabilities of the cortical excitability. Intracellular Ca^{2+} is critical for this process and is actively involved in the setting of the resting membrane potential and particularly in medial prefrontal cortex layer 2/3, pyramidal neurons express TRPM4, a non-selective cation channel permeable to monovalent cations and activated by intracellular calcium with a somatic and proximal-dendritic distribution. Using slice electrophysiology and local perfusion of pharmacological modulators of TRPM4 and cholinergic receptors, we study the participation of TRPM4 in modulation of local membrane potential in response to cholinergic modulation and how this impact the EPSP transmission. We found that somatic carbachol perfusion depolarizes layer 2/3 neurons, TRPM4 inhibition reduces this effect. Furthermore, the application of TRPM4 inhibitor obliterates the effect of carbachol on mEPSP. Additionally, after a train of synaptic stimulation, the application of TRPM4 inhibitors in the soma or in the distal dendrites obliterates the effect of carbachol in the eEPSP amplitude and slope. Altogether, our results suggest that TRPM4 participates in the cholinergic control local excitability with ensuing effects on synaptic transmission.

Disclosures: E. Leiva-Salcedo: None. **F. Navarro:** None. **F.A. Peralta:** None. **D. Riquelme:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.11/B48

Topic: B.04. Ion Channels

Title: NALCN channel is essential for pacemaking activity and burst discharges in substantia nigra dopamine neurons

Authors: *S. HAHN, M. PARK;
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Abstract: Dopamine neurons in the substantia nigra pars compacta (SNc) exhibit two major firing patterns: slow tonic firing and high-frequency phasic (burst) firing. Tonic pacemaking occurs spontaneously and regularly to maintain basal dopamine level, while phasic burst firing is evoked by glutamatergic afferents to increase dopamine transients in target areas *in vivo*. However, it is not elucidated whether NALCN ion channel is involved in these specific firing patterns in dopamine neurons. Since NALCN appears to be essential for the establishment of RMP and neuronal excitability, we investigated whether NALCN channels contribute to generation of tonic and phasic firings in nigral dopamine neurons. We observed that most dopamine neurons endogenously express NALCN mRNA. Replacement of extracellular Na^+ greatly influenced background leak currents and membrane potential. Despite the usage of TTX and Cs^+ which block Na_V and K_V channels, the substantial amount of Na^+ leak conductance remained, which was attenuated by inhibition of NALCN channels. NALCN inhibition also hyperpolarized membrane potential about 10 mV under the presence of TTX and ZD7288 which block Na_V and HCN channels. In addition, we found that, when NALCN was blocked, pacemaking was completely abolished and it can be reinstated by current injection. However, in this condition, glutamate-evoked burst firing was almost not generated. These results suggest that NALCN could play an important role not only in generation of pacemaker activity, but also in regulation of evoked burst discharges in nigral dopamine neurons.

Disclosures: **S. Hahn:** None. **M. Park:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.12/B49

Topic: B.04. Ion Channels

Support: CIHR Project Grant 159794

Title: Prolonged bursting evoked by reactive oxygen species in *Aplysia* neuroendocrine cells

Authors: *A. K. CHAUHAN, N. S. MAGOSKI;
Dept. of Biomed. and Mol. Sci., Queen's Univ., Kingston, ON, Canada

Abstract: Ion channels are essential for regulating the excitability and plasticity of neurons. In particular, non-selective cation channels (which pass Na^+ and K^+, and sometimes Ca^{2+}) elicit plateau potentials and persistent spiking in neurons responsible for learning, sensory processing, motor output, or neuroendocrine function. The bag cell neurons of the mollusc, *Aplysia*, have been used extensively to examine the regulation of secretion and excitability. Upon synaptic stimulation, these neuroendocrine cells undergo a prolonged period of enhanced excitability, known as the afterdischarge, during which hormones are released into the blood to initiate

reproduction. In part, a Ca^{2+}-permeable, Ca^{2+}-activated, voltage-dependent cation channel provides the depolarizing drive to sustain the afterdischarge. Furthermore, the afterdischarge is associated with both the activation of phospholipase C, which hydrolyzes phosphatidylinositol-4,5-bisphosphate into diacylglycerol (DAG), and the production of reactive oxygen species. As such, we tested if hydrogen peroxide (H_2O_2) impacts afterdischarge generation and if this is influenced by DAG. Under whole-cell voltage-clamp, perfusion of micromolar to millimolar concentrations of H_2O_2 resulted in an inward current in single cultured bag cell neurons. Preventing H_2O_2 reduction with mercaptosuccinate enhanced the current, while the reducing agent, dithiothreitol, lowered the response. In current-clamp, H_2O_2 resulted in depolarization followed by a burst, similar to a genuine afterdischarge. Treatment with cation channel blockers, 9-phenanthrol or clotrimazole, as well as the classical Na^+ channel antagonist, tetrodotoxin, largely attenuated both the H_2O_2-induced current and action potential firing. Moreover, in *ex vivo* desheathed bag cell neuron clusters, sharp-electrode current-clamp recording showed that H_2O_2 evoked a *bona fide* afterdischarge, implying that H_2O_2 may activate the cation channel that maintains the afterdischarge. Our lab recently published that 1-oleoyl-2-acetyl-sn-glycerol (OAG), a DAG analogue, potentiates this cation channel in cell-free patches. In the present study, bath-application of OAG enhanced the H_2O_2-induced current in whole-cell voltage-clamped cultured bag cell neurons. This would suggest that reactive oxygen species and phosphoinositol metabolites may function synergistically, and contribute to reproductive behaviour by promoting long-term bursting.

Disclosures: A.K. Chauhan: None. **N.S. Magoski:** None.

Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.13/B50

Topic: B.04. Ion Channels

Support: NIH Grant DK52766
NIH Grant DK106456
NIH Grant P30 DK084567

Title: Mechanosensitivity of the bacterial voltage-gated sodium channel NaChBac

Authors: *P. R. STREGE[1], A. MAZZONE[1], C. ALCAINO[1], C. A. AHERN[2], G. FARRUGIA[1], A. BEYDER[1];
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Abstract: Voltage-gated Na^+ channels (Na_Vs) are critical determinants of cellular electrical excitability. Na_Vs are present in tissues that have primary mechanical functions, such as the

heart, skeletal muscle, and gastrointestinal tract. Indeed, eukaryotic Navs are mechanosensitive, but the molecular mechanism of their mechanosensitivity is poorly understood due to their fast kinetics, large size, and limited structural information. Prokaryotic Navs are emerging as excellent models of eukaryotic Navs. One such prokaryotic Nav channel from *Bacillus halodurans*, NaChBac, is structurally, pharmacologically, and functionally similar to eukaryotic Navs. Further, NaChBac mutant T220A inactivates 70-fold slower than wild-type (WT), which allows for a close examination of its activation mechanism. We aimed to investigate NaChBac mechanosensitivity at the whole cell and single channel levels. We transiently expressed WT or T220A NaChBac in Piezo1 knockout (P1KO) HEK293 cells to exclude contribution from the mechano-gated channel. We next recorded Na^+ currents either by whole cell voltage clamp or as single channels in cell-attached patches with mechanical stimulation by shear stress or pressure clamp, respectively. Similar to eukaryotic Navs in previous studies, shear stress of WT and T220A NaChBac increased peak Na^+ current (ΔI_{PEAK}: WT +58.7±10.1%, T220A +39.0±6.8%), accelerated the activation kinetics ($\Delta\tau_A$: WT -39.3±3.8%, T220A -42.1±5.6%), and hyperpolarized the voltage-dependence of activation ($\Delta V_{1/2A}$: WT -4.4±0.6 mV, T220A -3.7±0.9 mV) and WT inactivation ($\Delta V_{1/2I}$: -3.7±1.1 mV) (n=7 cells each). At the single channel level, negative pressure (-30 mmHg) significantly increased T220A NaChBac open channel probability (P_O) when the voltage-dependent P_O was 0.2-0.3 (ΔP_O: +142.3±22.3%), but not at P_O <0.2 (+19.8±6.3%) or >0.3 (+9.4±5.1%). The pressure-induced P_O increase was due to an increase in the number of open events (+116.7%) alongside a decrease in the average duration of the closed events (Δt_{CLOSED}: -19.1%). In conclusion, bacterial Navs are good models of eukaryotic Nav mechanosensitivity, and our results support a Nav mechanosensitivity model in which force increases P_O by destabilizing the closed state. Supported by NIH Grants DK52766 (GF), DK106456 (AB), and the Mayo Clinic Center for Cell Signalling (P30 DK084567).

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Poster

462. Potassium Channels and Non-Selective Cation Channels

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 462.14/B51

Topic: B.04. Ion Channels

Support: CONACyT Fronteras de la CCiencia No. 1544

Title: Aminoglycosides differentially modulate acid sensing ionic channels (ASIC) depending on subunit composition of the channel

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Abstract: Acid-sensitive ion channels (ASICs) are involved in various processes such as epilepsy, cerebral ischemia pain perception, memory and learning among others, thus making them targets of interest. Aminoglycoside antibiotics were previously shown to inhibit ASIC currents in dorsal root ganglion neurons (DRGn) of the rat. In this work we report the effect of three aminoglycosides: gentamicin (Gen), tobramycin (Tbr) and kanamycin (Kan), on the ASIC currents. The experiments were performed using the patch clamp technique in the whole cell configuration to record native ASICs on DRGn and recombinant ASICs of different subunits (1a, 1b, 2a and 3) expressed in CHO K-1 cells. For the ASIC current activation a puff of acid pH (6.1, 5s) was used. In the co-application protocol both the acid pH and the drug were applied together during 5 s. In the pre-application the drug was applied 15s before the acid puff. In the pre-application channels interact with the drug in the closed state. In contrast, in the co-application the drug interacts with the channels in the open state. We found that in native ASICs, the co-application of Tbr, Gen and Kan produced a dose dependent inhibition of the ASIC currents, whilst during the pre-application Gen and Kan also produced an inhibition of the ASIC current whilst the Tbr increased the peak ASIC current up to 200% at 100 μM. Since the effect of Kan is of very low potency it was not further studied. In the heterologous expression system, Gen co-application has an inhibitory action in the peak of the current in ASIC2a and ASIC3 homomers. In both of them Gen also produced an increase in desensitization rate. Gen showed no action in ASIC1a homomers. In ASIC1a homomers the co- and pre-application of 100 μM Tbr produces an inhibition of the peak current. In ASIC1b tobramycin co-application has no effect but the pre-application inhibits the peak current and slows the desensitization rate. In ASIC2a homomers Tbr co-application produced an inhibition of the peak current, and a tendency to increase the peak current in the pre-application. In ASIC3 Tbr showed no action although a tendency to slow the desensitization rate was observed with the pre-application. In ASIC2a and ASIC2b heteromeric channels the co-application of Tbr inhibits the current and the pre-application produced an increase of the current. Our results showed that AG exerted a selective action depending on the subunit composition of the ASICs with a potentiating action while interacting with ASIC2a homomers and heteromers. The effect depends also on channels state. Thence analogues of these molecules could constitute new and valuable tools for the modulation of ASICs.

Disclosures: E. Soto: None. **A. Ortega-Ramírez:** None. **R. Felix:** None. **R. Vega:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.01/B52

Topic: B.06. Synaptic Transmission

Support: JSPS KAKENHI Grant Numbers 18K16495

Title: Histological examination at A11 of rat

Authors: *H. OZAWA[1], T. YAMAGUCHI[2], S. HAMAGUCHI[1], S. YAMAGUCHI[1], S. UEDA[2];
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Abstract: The A11 dopaminergic (DA)cell group is the only group that includes neurons innervating the spinal cord among the A8-A16 dopaminergic cell groups. Adysfunction of A11 dopaminergic systemis thought to contribute to the pathogenesis of restless legs syndrome. However, little is known regarding the neuronal composition, distributions, neurocircuitries of the A11 region. Revealing these histochemical properties of A11 neurons is being expected to elucidatethe mechanisms of regulating the spinal dopaminergic system.To determine the neuronal composition in the A11 region of adult male rat, we performed immunohistochemistry for neuronal markers such as tyrosine hydroxylase (TH), calcium binding proteins (CaBP) including calbindin (Calb) and parvalbumin (PV), and also for calcitonin gene-related peptide (CGRP), androgen receptor (AR), and estrogen receptors. To determine innervations of the A11 region, we also performed immunohistochemistry for dopamine beta hydroxylase (DBH) and corticotrophin-releasing factor (CRF).We found at least three types of neurons in the A11 region regarding expression of CaBP:TH(-)/ Calb(+), TH(+) /Calb(-), or TH(+) /Calb(+), whereas there were no PV-immunoreactive (IR) cell bodies. In combination with a tracer experiment using retrograde tracer Fluorogold (FG), we found FG-positive (FG(+)) neurons with a variety of neurochemical properties: FG(+)/TH(+)/Calb(+), FG(+)/TH(+)/Calb(-), FG(+)/TH(-) /Calb(+), FG(+)/TH(-)/Calb(-). In addition to these neuronal populations expressing CaBP, we also found CGRP positive cells, AR positive cells in the A11 region.For neuronal innervations of the A11 region, both Calb- and PV-IR processes were found throughout the entire A11 region, extending in varied directions depending on the level relative to bregma. We also found CRF-IR processes and DBH-IR processes with characteristic distributions within the A11 region. These findings indicate that the A11 region is composed of a variety of neurons that are distinct in their neurochemical properties, and suggest that the diencephalospinal dopamine system may be regulated at the A11 region by Calb-IR, PV-IR, DBH-IR, and CRF-IR processes,and at the terminal region of the spinal cord by Calb-IR processes derived from the A11 region.

Disclosures: H. Ozawa: None. **T. Yamaguchi:** None. **S. Hamaguchi:** None. **S. Yamaguchi:** None. **S. Ueda:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.02/B53

Topic: B.06. Synaptic Transmission

Support: MOST 107-2320-B-039-061-MY3
NHRI-EX108-10815NI

Title: The role of zinc in glycinergic synaptic transmission and hyperekpleixa

Authors: *D. WU[1], N. ZHOU[2];
[1]China Med. University, Grad. Inst. of Biomed. Science,, Taichung, Taiwan; [2]Grad. Inst. of BioMedical Sci., China Med. Univ., Taichung, Taiwan

Abstract: The free Zn^{2+} is not only a contributing factor of neuronal death after stroke, but also plays an important role in regulating synaptic transmissions by modulation of synaptic receptors and ion channels. Zn^{2+} modulates different channel receptors, such as NMDA receptors, GABAA receptors, glycine receptors (GlyRs), and voltage-gated Ca2+ channels. Among these, GlyRs are bidirectionally modulated by Zn2+: low concentrations (from nanomolar to low micromolar levels) of Zn^{2+} potentiate GlyR currents, whereas high concentrations (>~10 micromolar) inhibit GlyR functions. GlyRs mainly mediate the fast inhibitory synaptic transmission in the spinal cord and brain stem. The deficits of GlyR functions are directly associated with human hyperekplexia, which is characterized by exaggerated startle responses upon the unexpected stimuli. It has been reported that the $Glra1^{D80A}$ knockin mice, in which the potentiation of GlyR was supposed to be eliminated, showed only mild symptoms resemblance to the human startle diseases. However, more recent studies argued that the D80A mutation failed to affect Zn2+-mediated potentiation on GlyR functional, making it inconclusive whether Zn2+ modulation is critical for GlyR-mediated functions and synaptic transmission.Our recent study has found that the human hyperekplexia missense mutation in the GlyR α1 subunit, W170S, caused almost complete loss of Zn2+-mediated potentiation, and these results have been confirmed by several other groups. Based on our previous studies, we generated W170S knockin mice. The phenotypes of W170S mice appeared from 14 days to 16 days after birth. They showed reduced the right reflex abnormal gait and tremor. A sudden sound from a clap by the observer led to the generalized muscle contractions and the fall over. The severity of symptoms gradually increased since the initiation. Usually, the homozygous died in 4 to 5 postnatal weeks even with intensive care. The mRNA level of Glra1 in the cortical cortex and spinal cord from WT, heterozygous and homozygous Glra1(W170S) mice from the same litters were not significantly different by performing Q-PCR assay. We further detected the protein expression levels of GlyRs α1 in the neocortex and spinal cord. The preliminary results indicated that the

expression level of GlyRs α1 in the spinal cord showed a mild decrease in homozygous but not heterozygous Glra1(W170S) compared with their WT littermates. Taking advantage of this knock-in mouse model, we will unveil whether Zn2+ modulates synaptic transmission in glycinergic synapses and how these modulations are linked to human diseases.

Disclosures: D. Wu: None. **N. Zhou:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.03/B54

Topic: B.06. Synaptic Transmission

Support: NFR grant 163211/V50
CMBN grant 142039

Title: Dendritic localisation and exocytosis of NAAG in the rat hippocampus

Authors: K. NORDENGEN[1,4], ***C. MORLAND**[2,1], B. S. SLUSHER[5], V. GUNDERSEN[6,1,3]; [1]Dept. of Mol. Med., [2]Dept. for Pharm., [3]Inst. of Clin. Med., Univ. of Oslo, Oslo, Norway; [4]Dept. of Neurol., Akershus Univ. Hosp., Lørenskog, Norway; [5]Johns Hopkins Drug Discovery, Baltimore, MD; [6]Dept. of Neurol., Oslo Univ. Hosp., Oslo, Norway

Abstract: While a lot is known about classical, anterograde neurotransmission, less is known about the mechanisms and molecules involved in retrograde neurotransmission. Our electron microscopic immunogold data suggests that N-acetylaspartylglutamate (NAAG), the most abundant dipeptide in the brain, act as a retrograde transmitter in the hippocampus. NAAG was predominantly localised in dendritic elements of glutamatergic synapses, where it was present in close proximity to synaptic-like vesicles. In hippocampal slices, NAAG was depleted from postsynaptic dendritic elements during neuronal stimulation induced by depolarising concentrations of potassium or by exposure to glutamate receptor agonists. The depletion was completely blocked by botulinum toxin B, and strictly dependent on extracellular calcium, indicating exocytotic release. In contrast, NAAG levels in presynaptic glutamatergic nerve terminals and GABAergic pre- and postsynaptic elements were very low. In these compartments depolarisation or glutamate receptor agonists, did not affect the levels of NAAG, indicating that NAAG was released exclusively from postsynaptic elements of glutamatergic synapses. Together these data suggest a possible role for NAAG as a retrograde signalling molecule at glutamatergic synapses via exocytotic release.

Disclosures: K. Nordengen: None. **C. Morland:** None. **B.S. Slusher:** None. **V. Gundersen:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.04/B55

Topic: B.06. Synaptic Transmission

Support: MOE2015-T2-2-095
MOE2017-T3-1-002

Title: Cell-type specific serotonergic modulation of the claustrum

Authors: *K. L. L. WONG, G. J. AUGUSTINE;
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Abstract: The claustrum is a thin, long structure that forms dense and reciprocal connections with many other brain regions. Although serotonergic inputs to the claustrum have been reported (Histochem J. 28:747; J Comp Neurol. 526:2428), the role of serotonin in claustral function is unknown. To address this question, we performed whole-cell patch clamp recordings from claustral neurons in brain slices, while either applying serotonin by pressure application or releasing endogenous serotonin by photostimulating serotonergic terminals via Channelrhodopsin-2. Six different types of claustral neurons were classified according to their intrinsic electrical properties. Approximately 75% of all these neurons responded to serotonin application, even in the presence of blockers of glutamate receptors (kynurenic acid; 100 μM) and GABA receptors (GABAzine; 10 μM) to eliminate potential upstream synaptic responses. In all three types of claustral projection neurons, serotonin evoked a long-lasting outward current (V_h = -60 mV) that was caused by a potassium conductance increase. Photostimulation-induced release of endogenous serotonin evoked a similar outward current response from claustral projection neurons. This response was mediated by at least in part by 5HTR-2C serotonin receptors, because it was reduced by a specific blocker of this receptor (RS1002221; 5 μM). Claustral interneurons exhibited a heterogenous mix of responses to serotonin application. VIP interneurons produced an inward current at -60 mV. This response was mediated by 5HTR-3A receptors, because it was eliminated by the 5HTR-3A blocker granisetron (1 μM). In contrast, SST and PV neurons showed either inward or outward current responses. We conclude that serotonin produces a diversity of postsynaptic actions within the claustrum: projection neurons are largely inhibited by serotonin, while local interneurons are either excited or inhibited by serotonin. On balance, the net effect of this serotonergic modulation is to inhibit claustral output. Thus, serotonin could play a prominent role in gating claustrum function *in vivo*.

Disclosures: K.L.L. Wong: None. **G.J. Augustine:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.05/B56

Topic: B.06. Synaptic Transmission

Title: Neuronal cFOS activation in response to amphetamine and methamphetamine identified with whole brain clearing

Authors: *T. P. WIGSTROM[1], S. M. UNDERHILL[1], M. S. COLT[1], S. WILLIAMS AVRAM[2], T. USDIN[2], S. G. AMARA[1];
[1]Lab. of Mol. and Cell. Biol., Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Systems Neurosci. Imaging, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Acute exposure to amphetamine (AMPH) and methamphetamine (METH) has been extensively linked to the activation of mesocorticolimbic circuits through their ability to modulate dopaminergic and glutamatergic neurotransmission. The two drugs differ in their elicited behavioral outcomes, therapeutic utility, and potential for addiction despite only differing by a single methyl group. Upon entry into dopamine neurons, both drugs activate similar G-protein-linked signaling pathways through the activation of an intracellular GPCR for trace amines, TAAR1. However, we have recently observed that METH can activate these same signaling pathways in cell types which lack the dopamine transporter (DAT), suggesting that METH can enter cells through a different mechanism that does not involve transport by the DAT. To further investigate this hypothesis, we examined the anatomical distribution of activated neurons in the brains of mice exposed to AMPH and METH using the whole brain clearing technique iDISCO (immunolabeling-enabled 3D imaging of solvent-cleared organs). We identified activated neurons in the brain by immunostaining for activated cFos, an immediate early gene transcription factor that is highly responsive to membrane depolarization and thus provides a readout of neuronal activation. Saline, AMPH (2 mg/kg), or METH (2 mg/kg) solutions were administered by i.p. injection into adult (12-24 w) C57/bl6 male and female mice. At 2 hrs, the mice were anesthetized and perfused with 4% paraformaldehyde. The whole brains were immunolabeled for cFOS and then cleared with dichloromethane and dibenzyl ether. We imaged the brains with a light sheet microscope and analyzed the images with Arivis software. We identified eighteen regions of interest, with the majority involved in either basal ganglia or limbic circuits. Differences in cFos activation were observed between vehicle control and AMPH brains. Furthermore, METH brains exhibited new regions of activation compared to the AMPH brain. These data highlight the divergent circuit activation mediated by these closely-related psychostimulants that may contribute to the differences in the pharmacological and behavioral profiles observed for AMPH and METH.

Disclosures: **T.P. Wigstrom:** None. **S.M. Underhill:** None. **M.S. Colt:** None. **S. Williams Avram:** None. **T. Usdin:** None. **S.G. Amara:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.06/B57

Topic: B.06. Synaptic Transmission

Support: NIH grant 1R21DA045889-01A1

Title: Methamphetamine sensitization facilitate inhibitory currents in pyramidal neurons from the medial prefrontal cortex

Authors: *M. ARMENTA-RESÉNDIZ[1], A. LAVIN[2];
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Abstract: Background: Chronic methamphetamine (METH) exposure has become a serious problem throughout the world and has been connected to several harmful medical complications, particularly hypofrontality and deficits in cognition. Here we propose that METH sensitization increases inhibitory transmission in the prefrontal cortex (PFC) through a D1R activation of fast-spiking parvalbumin-positive interneurons. The outcome of interneuron over-activation will be an imbalance in excitation/inhibition homeostasis resulting in hypofrontality and cognitive deficits.Methods: We use whole-cell recordings to determine the effects of METH sensitization (1 mg/kg 1st and 7 or 14 day and 5 mg/kg 2-6 or 2-13 days) on the inhibitory activity in prelimbic (PL) layer 5 pyramidal neurons of slices from medial prefrontal cortex (mPFC) in Cre+ PV Long-Evans male and female rats. We evaluate cognitive activity with Novel Object Recognition (NOR) and working memory tests (WM). Results: Neurons from animals repeatedly exposed to METH show a significant increase in the amplitude of sIPSCs after 7 or 14 days of METH. Also, they show a significant increase in frequency at 14 days as well as significant increases in the current needed for evoking a minimum response. Moreover, bath administration of the antagonist D1 SCH 23390 blocks the METH effect in amplitude but not in the frequency of the events. We also found that METH causes significant deficits in the NOR test for temporal order memory.Conclusions: In summary, METH sensitization enhances the inhibitory transmission in PL layer 5 pyramidal neurons of the mPFC and causes cognitive impairments. D1 antagonism is able to reduce the postsynaptic effects mediated by METH exposure.

Disclosures: **M. Armenta-Reséndiz:** None. **A. Lavin:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.07/B58

Topic: B.06. Synaptic Transmission

Support: NIH NCRR S10 OD010662

Title: Is it time to rename the neuropeptide processing enzyme Neurolysin (EC3.4.24.16)?

Authors: *K. D. PHILIBERT[1], X. SHAO[1], M. J. GLUCKSMAN[2];
[1]Ctr. for Proteomics and Mol. Therapeut., Rosalind Franklin Univ. of Med. and Sci., North Chicago, IL; [2]Biochem. & Mol. Biol., Chicago Med. School/RFUMS, North Chicago, IL

Abstract: Neuropeptides modulate intercellular communication for proper metabolic activity, cell differentiation and growth in a neurobiological context. Alterations in expression or processing of neuropeptides produces deleterious neuropathophysiologic processes. It is the neuropeptide processing enzymes that form a nexus in the synapse for regulating signaling in the extracellular milieu through its control of peptide neurotransmitters. Though originally assigned numbers by the Enzyme Commission, more descriptive names were assigned ~25 years ago when fewer neuropeptides were known but today these names are misnomers and do not adequately convey function. Two closely related neuropeptide processing enzymes that cleaved 6-9 different substrates at the same location, EC3.4.24.15 (EP24.15; thimet oligopeptidase) and EC3.4.24.16 (EP24.16; neurolysin), were distinguished solely by an alteration in the bond hydrolyzed in neurotensin; hence, the designation Neurolysin. Through our neuromics discovery pipeline to unveil new substrates for processing enzymes, the repertoire of neuropeptide regulation has expanded beyond the initial six to nine observations in the past. Utilizing biochemical, structural, and systems-based proteomic approaches including in silico molecular modeling, mass spectrometry, enzyme kinetics, and X-Ray crystallography, we have demonstrated substrates for EP24.16 that differ substantially from the closely related EP 24.15 both in the detailed cleavage sites as well as whether a peptide can be degraded and thus is a true substrate. Several examples include the neuroprotective, hybrid neuropeptide substrate Colivelin and the EP 24.15 cleaved reproductive peptide Phoenixin while gonadotropin inhibitory neuropeptide RFRP-3 exhibits different cleavage sites. Interestingly, Xenin 8, a gut peptide, with a C-terminal sequence very similar to Neurotensin, is cleaved at the same site by both EP24.15 and EP24.16 enzymes. This has further ramifications as several processing enzymes can act upon the same neuropeptide and a given neuropeptide can be a substrate for several neuropeptide processing enzymes. Furthermore, the fragments produced by the action of these enzymes themselves can have varied and novel functions such as the degradation of the decapeptide GnRH responsible for reproduction; the GnRH1-5 fragment produced has a different receptor

and downstream signaling from it's parent peptide. With the discovery of novel neuropeptides and their functions coupled with advanced technological methodologies, one must be cautious with utilizing older, misleading enzyme names for neuropeptide processing enzymes.

Disclosures: K.D. Philibert: None. **X. Shao:** None. **M.J. Glucksman:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.08/B59

Topic: B.06. Synaptic Transmission

Support: NIDA Intramural Research Program

Title: Sigma-1 receptor control of cocaine-induced endocannabinoid signaling via inhibition of extracellular vesicle release in the ventral tegmental area

Authors: *D. I. DRYANOVSKI[1], Y. NAKAMURA[2], T.-P. SU[3], C. R. LUPICA[4];
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Abstract: Endogenous cannabinoids (eCB) are signaling lipids released from neurons that retrogradely activate cannabinoid CB1 receptors (CB1R) on axon terminals to limit neurotransmitter release. 2-arachidonoylglycerol (2-AG) is an eCB that is synthesized from membrane phospholipids by the enzyme diacylglycerol lipase-α (DGLα). Our previous work has demonstrated that cocaine stimulates 2-AG synthesis in rat midbrain dopamine neurons to increase their activity via inhibition of GABAergic synapses, or disinhibition. However, mechanisms for 2-AG release are unknown. Here, we confirm that cocaine stimulates the synthesis of 2-AG in the mouse midbrain dopamine neurons and identify a mechanism whereby 2-AG is localized to non-synaptic extracellular vesicles (EVs) that are released when cocaine binds to the Sigma-1 receptor (σ1R). The σ1R resides on the mitochondria-ER interface membrane, serving as a protein chaperone, and plays a role in controlling calcium signaling from the ER to the mitochondria. Under basal conditions, the σ1R is bound to ADP-ribosylation factor 6 (ARF6), a small GTPase. Cocaine binding to the σ1R leads to dissociation of the σ1R/ARF6 complex and activation of myosin light chain kinase (MLCK), which is permissive to EV release. Genetically eliminating or pharmacologically inhibiting σ1Rs prevented cocaine-induced 2-AG release. However, pharmacological inhibition of σ1Rs had no effect on depolarization-induced suppression of inhibition (DSI) at GABAergic synapses on midbrain dopamine neurons, and experiments are planned to determine whether DSI is disrupted in σ1R knockout mice. We also found that the synthesis and tonic release of 2-AG is not altered in σ1R knockout mice,

suggesting specificity for cocaine-facilitated 2-AG release. Our results demonstrate that cocaine-mediated 2-AG signaling is controlled by the σ1R-ARF6-MLCK pathway and shed new light on the mechanisms through which cocaine promotes eCB release. These results could lead to potential novel treatments for cocaine addiction.

Disclosures: D.I. Dryanovski: None. **Y. Nakamura:** None. **T. Su:** None. **C.R. Lupica:** None.

Poster

463. Synaptic Transmission: Modulation and Mechanisms II

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Program #/Poster #: 463.09/B60

Topic: B.06. Synaptic Transmission

Support: NIH R01 AG061787 to J.N.S
2018 NARSAD Young Investigator Grant to Y-Z.W

Title: Extracellular vesicles promote bidirectional synaptic communication through CamKII

Authors: *Y.-Z. W. WANG[1], S. N. SMUKOWSKI[1], C. PIOCHON[2], E. BOMBA-WARCZAK[1], Q. HE[3], S. A. MARSHALL[1], E. T. BARTOM[1], A. SHILATIFARD[1], A. CONTRACTOR[4], J. N. SAVAS[1];
[2]Dept. of Physiol., [1]Northwestern Univ., Chicago, IL; [3]physiology, [4]Physiol., Northwestern Univ. Dept. of Physiol., Chicago, IL

Abstract: Extracellular vesicles (EVs) are specialized organelles that extrude and transfer proteins and RNAs between cells. Neuronal EVs have been identified, but their properties and functional relevance remain poorly understood. We performed transcriptomic and proteomic analyses and unexpectedly identified EVs as critical regulators of the early molecular events underlying NMDAR-dependent synaptic strengthening. Rapidly after NMDAR activation the core EV proteins Alix and Tsg101 are synthesized, localize to synapses, and promote EV release from neurons. Synaptic activity-induced EVs have similar properties to EVs produced by other cells types, and proteomic analysis revealed they contain phosphorylated CamKII and other synaptic proteins. EVs can be taken up by nearby neurons and induce bi-directional synaptic signaling via subsequent phosphorylation of CamKII in unstimulated neurons. Blocking ceramide production, which is required for EV biogenesis, inhibited the enhancement of mEPSC amplitudes after glycine treatment. Taken together, EVs appear to play an active role in the process of synaptic strengthening.

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Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.10/B61

Topic: B.07. Synaptic Plasticity

Support: DFG-SFB779

Title: Extracellular matrix controls principal cell excitability and synaptic plasticity in the hippocampus

Authors: I. SONG[1], J. SINGH[2], A. WIRTH[3], D. MINGE[4], R. KAUSHIK[1], M. FERRER-FERRER[1], J. MITLÖHNER[2], A. ZEUG[3], C. HENNEBERGER[4], E. PONIMASKIN[3], R. FRISCHKNECHT[5,2], C. J. SEIDENBECHER[2], ***A. DITYATEV**[1,6];
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Abstract: The extracellular matrix (ECM) regulates neural development and activity of neural and immune cells in mature brains. Paradoxically, ECM attenuation is reported either to enhance or to impair synaptic plasticity. Here, we uncover molecular mechanisms behind this dual action. We demonstrate that enzymatic attenuation of ECM by chondroitinase ABC (ChABC) decreases CA1 pyramidal cell excitability and thus restrains long-term potentiation (LTP) in CA3-CA1 synapses. This effect is mediated by a loss of ECM proteoglycan brevican, triggering increased cell surface expression of small conductance (SK) Ca^{2+}-activated K^+ channels through a mechanism involving metabotropic glutamate receptors ($mGluR_{III}$) and protein kinase A. Blocking this mechanism restores principal cell excitability and LTP in brevican knockout mice, and leads to supranormal signaling through β1 integrins and NMDA receptors, which augment LTP after enzymatic attenuation of ECM. Thus, ECM molecules - enriched in perineuronal nets associated with fast-spiking perisomatic interneurons, but also broadly expressed as the perisynaptic ECM enveloping principal neurons - homeostatically control the excitability of the latter cells and predisposition of excitatory synapses to undergo functional modifications.

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Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.11/B62

Topic: B.06. Synaptic Transmission

Support: NIH Training Grant T32 MH064913-15

Title: The role of Itgβ3 in nucleus accumbens function

Authors: *A. N. JAMESON[1], A. CARNEIRO[2], D. G. MCMAHON[3,2,1], B. A. GRUETER[4,2,1]; [1]Vanderbilt Brain Inst., [2]Pharmacol., [3]Biol. Sci., [4]Anesthesiol., Vanderbilt Univ., Nashville, TN

Abstract: Stress disorders, like depression, anxiety, and substance use disorder, are regulated by serotonin (5-HT). The dorsal raphe nucleus (DRN), the major site for neuronal 5-HT synthesis, sends projections to the nucleus accumbens (NAc). Synaptic adaptations in the NAc correlate with changes in mood and reward, key components of stress disorders. A subpopulation of DRN projection neurons express the β3 subunit of the integrin αvβ3 receptor (Itgβ3). Itgβ3 regulates extracellular 5-HT concentration by modulation of 5-HT transporters. Mice lacking Itgβ3 have increased vulnerability to chronic stress, implicating a role for Itgβ3 in behavior. Furthermore, the Itgβ3 receptor contributes to cocaine-reinstated drug-seeking by regulating AMPAR surface expression in the NAc. However, how Itgβ3 regulates 5-HT and excitatory transmission in the NAc, and contributes to maladaptive reward behaviors is unknown. Itgβ3 is only expressed in a subpopulation of 5-HT neurons, suggesting that it confers a specific function to this neuronal population. Using a mouse line with selective deletion of Itgβ3 within 5-HT neurons, we are investigating its role in the DRN to NAc circuit. Using acute brain slice whole-cell patch-clamp electrophysiology, we have characterized how Itgβ3 contributes to 5-HT synaptic transmission as well as glutamatergic transmission. Our data suggests that Itgβ3 in 5-HT neurons modulates both excitatory and 5-HT synaptic transmission in the NAc. Behavioral assessment of the contribution of Itgβ3 within this circuit is ongoing. Taken together, the behavioral and electrophysiological assessment will provide an understanding of the mechanistic contribution of Itgβ3 within the 5-HT circuit to stress disorders.

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Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

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Program #/Poster #: 463.12/B63

Topic: B.06. Synaptic Transmission

Support: NIMH Grant R01MH104638
VA Merit Award I01 BX001374
NIH-NIHMS T32-GM081740
SPARC Graduate Research Grant from the Office of the Vice President for Research at the University of South Carolina

Title: Acetylcholine differentially modulates cortical and thalamic input to the basolateral amygdala

Authors: *S. C. TRYON[1], J. X. BRATSCH-PRINCE[1], J. W. WARREN[1], G. C. JONES[1], M. A. WILSON[1,2], A. J. MCDONALD[1], D. D. MOTT[1];
[1]Dept. of Pharmacology, Physiol. and Neurosci., Univ. of South Carolina Sch. of Med., Columbia, SC; [2]Columbia VA Hlth. Care Syst., Columbia, SC

Abstract: The basolateral amygdala (BLa) receives glutamatergic input from cortical and subcortical regions and cholinergic input from the basal forebrain. Acetylcholine, released by this cholinergic input, can modulate emotional memory encoding and consolidation. We have previously reported that pharmacological activation of muscarinic receptors (mAChRs) suppresses cortical input to the BLa and that the extent of this muscarinic inhibition varies between individual rodents. Furthermore, differences in muscarinic inhibition correlate with individual differences in cued fear learning and extinction in rats, suggesting that differences in cholinergic signaling may underlie individual variation in the susceptibility to fear memory disorders. To further explore the mechanism of cholinergic inhibition we used brain slice electrophysiology and optogenetics to investigate the effect of optogenetically released ACh at prelimbic (PL) and thalamic (THAL) inputs to BLa. Released ACh significantly suppressed both cortical and thalamic input to BLa. Theta burst stimulation of cholinergic input was effective at producing inhibition, in line with the reported firing pattern of basal forebrain neurons. ACh-mediated inhibition of cortical input was blocked by atropine, indicating that it was muscarinic receptor-mediated. To investigate inhibition at specific input pathways, we optogenetically stimulated PL or THAL input and pharmacologically activated mAChRs with muscarine. Muscarine produced significantly stronger inhibition of PL than THAL input. Furthermore, inhibition in these two pathways was mediated through different mechanisms. Inhibition of PL input was directly produced by presynaptic M3 mAChRs, whereas inhibition of THAL input was mediated by retrograde endocannabinoid signaling engaged by postsynaptic M3 mAChRs.

Reflecting these distinct mechanisms, muscarinic inhibition in these two pathways displayed distinct frequency dependence. During low frequency stimulation (1-10 Hz) of input pathways, muscarinic inhibition remained intact throughout the 10 pulse stimulus train. However, during high frequency stimulation (20-40 Hz), inhibition of THAL input strengthened, whereas inhibition of PL input was relieved. Furthermore, at PL inputs we found that postsynaptic mAChRs enhanced NMDA currents, suggesting that the PL input that overcomes muscarinic inhibition may selectively enhance plasticity. Overall, these findings suggest a mechanism through which ACh can specifically enhance signaling and plasticity during high frequency (gamma) activity at PL input and regulate fear memories.

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Poster

463. Synaptic Transmission: Modulation and Mechanisms II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 463.13/B64

Topic: B.06. Synaptic Transmission

Support: NIH Grant 1R01 AA026531

Title: Ethanol modulation of inhibitory circuits in the basolateral amygdala

Authors: *S. MUNSHI, J. G. TASKER;
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Abstract: Both clinical and pre-clinical studies have shown an effect of alcohol consumption on fear conditioning. The basolateral amygdala (BLA), which consists of both glutamatergic projection neurons and GABAergic interneurons, is known to play an important role in the development and regulation of fear memory formation. The overall excitatory activity of the BLA is tightly regulated by GABAergic interneurons, which play an important role in fear memory regulation. Thus, determining the effect of alcohol on the activity of local GABA circuits in the BLA is crucial to understanding the neuronal basis for the neurophysiological and fear-related behavioral effects of alcohol consumption. The alcohol regulation of GABAergic interneuron circuits of the adult BLA is not well understood. Therefore, in the present study, we used *ex vivo* whole-cell patch-clamp recordings from BLA pyramidal neurons in amygdala slices of adult male Wistar rats (8 - 10 weeks of age) to investigate the effects of acute ethanol application on GABAergic inhibitory postsynaptic currents (IPSCs). Our exploratory findings showed that ethanol increases the frequency of both spontaneous and miniature IPSCs without affecting IPSC amplitude or decay time. Preliminary experiments suggest that the ethanol response is specific to parvalbumin neurons. These data suggest that ethanol causes a spike-

independent, presynaptic modulation of GABA inhibitory inputs from parvalbumin interneurons to BLA principal neurons in the adult male rat.

Disclosures: **S. Munshi:** None. **J.G. Tasker:** None.

Poster

464. Cellular Mechanisms of Oscillations

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 464.01/B65

Topic: B.09. Network interactions

Support: MOST Taiwan ROC 105-2112-M-001-017-MY3.

Title: Astroglial role in synchronized persistent neuronal activities

Authors: *R. KUMAR[1], Y.-T. HUANG[2], S.-F. TZENG[3], C.-K. CHAN[1];
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Abstract: Cognitive processes are related to synchronization and propagation of firing activities in neuronal systems. These temporal coordinations in the form of burst-firings occur by sequential activation of cell assemblies (1) and are widely observed *in vivo* and *in vitro* brain tissue conditions. This process of sequential cell assembly could be physiological (2) or pathological (3). Still, the underlying mechanism behind such coordinated behavior remains unclear. Lines of evidence indicate astroglial network could extend neuroglial interplay by allowing information processing and integration in large number of neurons. It is now conceivable that origin and sustenance of coordinated temporal dynamics in neurons may not solely ruled by neuron-neuron interaction. Recent findings on neuron-astrocyte synaptic interaction (4) further supports, neuro-glial networking could be the effective mechanism behind such coordinated activities. However, the collective dynamics interplay between the two cell types had been speculative due to absence of robust astrocyte-specific tools so far. Current advancement in genetically encoded indicators specifically designed for studying astrocytes enables us to investigate their interactions more closely. Here we report our findings obtained from cortical cultures developed on a multi-electrode arrays (MEA) system. Employing astrocyte-specific genetically encoded calcium indicators(GECI) with MEA, we found that astroglial network respond to neuronal persistent synchronized activities through synchronized calcium elevation. Based on previous studies (5), positive feedback from synaptic glutamate release mediates persistent neuronal activities. Through pharmacological manipulation of glutamate transporters, it was found that persistent activities are tightly regulated by astrocytic glutamate transporters (GLT-1). Therefore, it is indicative that neuron-astrocyte interaction through astroglial glutamate transporter system could be an important regulatory mechanism

whose function/dysfunction could contribute to context-dependent/abnormal information integration in neuronal circuits.
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Poster

464. Cellular Mechanisms of Oscillations

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ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: B.09. Network interactions

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Title: Persistence of neuronal representations through time and damage in the hippocampus

Authors: *W. G. GONZALEZ, H. ZHANG, A. HARUTYUNYAN, C. LOIS;
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Abstract: It is not known how neurons encode memories that can persist up to decades. To investigate this question, we performed long-term simultaneous bilateral imaging of neuronal activity in the hippocampus of freely moving mice. From one day to the next ~40 % of neurons changed their responsiveness to cues; however, thereafter only an additional 1 % of cells changed for each additional day. Despite the apparent instability between days, field responses of CA1 neurons are very resilient to lack of exposure to the task or lesions to CA1. Although a small fraction of individual neurons retain their responses over weeks, groups of neurons with inter- and intrahemispheric synchronous activity had stable responses. Neurons whose activity was synchronous with a large group of neurons were more likely to preserve their responses across multiple days. These results suggest that although information stored in individual neurons is relatively labile, representations of a familiar environment can be stable in networks of synchronously active neurons.

Disclosures: **W.G. Gonzalez:** None. **H. Zhang:** None. **A. Harutyunyan:** None. **C. Lois:** None.

Poster

464. Cellular Mechanisms of Oscillations

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 464.03/B67

Topic: B.09. Network interactions

Support: DFG Grant Ha4466/11-1

Title: Interneuronal control of early oscillatory activity in the olfactory bulb of neonatal mice

Authors: ***J. K. KOSTKA**, I. L. HANGANU-OPATZ;
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Abstract: Precisely-tuned interplay between pyramidal neurons and interneurons during early development enables the maturation of neuronal networks and their coordinated activity as well as behavioral performance at adulthood. In the olfactory bulb (OB), oscillatory activity in different frequency bands is considered to be important for odor sampling, discrimination, and learning. However, while the sense of olfaction is already functional from birth, the OB network activity at this age differs substantially from adult patterns. Recently, we have shown that in the developing OB, pyramidal neurons, i.e mitral and tufted cells (MTCs), play a crucial role in the generation of neonatal continuous respiration-driven oscillations (2-4 Hz) and discontinuous theta bursts (4-12 Hz). In addition, odor sampling induces beta band (15-30 Hz) activity in the neonatal OB, while gamma oscillations (30-100 Hz), linked to odor discrimination, are still absent during the first postnatal weeks. The role of interneurons for the generation of oscillatory patterns in the OB during development remains largely unknown. To close this knowledge gap, we combine optogenetic manipulation of genetically-defined interneuron subtypes in the OB of neonatal mice (postnatal day (P) 8-10) with extracellular recordings of single unit activity and local field potentials *in vivo*. Optogenetic stimulation of $Gad2^{+}$ interneurons leads to a strong decrease in MTC firing as well as a decrease of oscillatory activity in the theta and beta band in the OB. In contrast, inhibition of the same cell populations increases theta band activity as well as the power of the respiration-related rhythm. These results indicate an important role of local interneuron-MTC interactions in shaping coordinated activity in the developing OB.

Disclosures: **J.K. Kostka:** None. **I.L. Hanganu-Opatz:** None.

Poster

464. Cellular Mechanisms of Oscillations

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 464.04/B68

Topic: B.09. Network interactions

Title: Cholinergic induced slow wave oscillation in the claustrum *in vitro*

Authors: *T. J. BAL, C. MONIER, G. OUANOUNOU;
Integrative and Computat. Neurosci., Paris-Saclay Inst. of Neurosci. (NeuroPSI), CNRS/Paris-Sud University, UMR9197, Gif Sur Yvette, France

Abstract: The claustrum (and the endopiriform nucleus) form a complex containing a small proportion of interneurons and a majority of far-projecting excitatory claustrocortical neurons that lay deep below the insular cortex. It is the most reciprocally connected structure in the brain and receives cholinergic and a variety of neuromodulatory inputs from subcortical structures (Goll et al., 2015). Its functional role remains largely unknown. The claustrum has been proposed to be a central integrator for the unified sense of cognition (Crick & Koch, 2005), a hub for attention (Atlan et al., 2018), for multi-sensory binding, and may modulate the synchronization of neocortical slow-wave activity (Narikiyo et al., bioarXiv 2018) or enhance synchronized oscillations between cortical areas (see Vidyasagar & Levichkina, 2019). Little is known on the claustrum circuit properties or on its cell-types: the membrane and synaptic properties, the sensitivity to neuromodulation, and spontaneous states of activities. We use techniques that preserve recurrent slow oscillations (resembling the in vivo up & down states) in cortical circuits in mouse brain slices. In a slice that contains parts of the claustrum and neocortex, we found that the claustrum generates two different types of activities. i) A spontaneous and moderate spiking discharge in principal neurons and interneurons generated by background synaptic activity appears randomly, can last hundreds of milliseconds to seconds, and returns to quiescent periods. ii) Application of the cholinergic agonist carbachol induces in about half of the experiments a robust 0,3-1 Hz rhythmic recurrent network oscillation characterized by the occurrence of compound excitatory and inhibitory postsynaptic potentials and spike discharge. We are exploring the mechanisms of this claustrum slow-wave activity: Does it result solely from the interactions of neurons within the claustrum, although there are few direct connections between its principal cells (Kim *et al.*, 2016), and/or is it due to synaptic loops between the claustrum and neocortex, such as the adjacent insular cortex, or the entorhinal cortex that spontaneously generates Up & down states in the same slice?

Disclosures: **T.J. Bal:** None. **C. Monier:** None. **G. Ouanounou:** None.

Poster

464. Cellular Mechanisms of Oscillations

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Topic: B.09. Network interactions

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Title: Conditions for and detectability of extremely fast oscillations in neuronal activity

Authors: R. HELIN[1], S. ESSINK[2], H. BOS[3], E. HAGEN[4], M. HELIAS[2], J. SENK[2], T. TETZLAFF[2], S. J. VAN ALBADA[2], M. DIESMANN[2], S. GRÜN[2], ***H. E. PLESSER**[1,2];
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Abstract: While validating a biologically motivated network model [1] against some 150 simultaneously recorded experimental spike trains [2] we observed qualitative differences in the raster plots and power spectra of the two. The network model exhibits extremely fast oscillations at over 200 Hz visible as a peak in the power spectrum and as narrow, closely spaced vertical stripes in the spike raster plot, which are not visible in raster plots of the experimental data. We wondered if the extremely fast oscillations may be overlooked in experimental data due to lack of data or if they only exist due to specific properties of the network model.
Early theoretical studies of simple random networks identified the inhibition-dominated excitatory-inhibitory loop as the origin of these oscillations and proposed parameter regimes avoiding the oscillations [3]. Today, both analytical and simulation tools are available to investigate more complex multi-layered network models.
This allows us to investigate extremely fast oscillations in a well-established cortical microcircuit model [1,4] comprising four cortical layers with an excitatory and inhibitory population each.

After confirming that the extremely fast oscillations are not simulation artifacts, we explored how the number of spike trains sampled from simulations affects the detectability of gamma-band and of extremely fast oscillations. We further found that extremely fast oscillations do not occur for certain distributions of synaptic delays.
[1] Potjans TC, Diesmann M. Cereb Cortex 24:785 (2014). [2] Brochier T, Zehl L, Hao Y, Duret M, Sprenger J, Denker M, Grün S, Riehle A. Sci Data 5:180055 (2018) [3] Brunel N. J Comput Neurosci 8:183 (2000). [4] Bos H, Diesmann M, Helias M. PLoS Comput Biol 12:e1005132 (2016).

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Poster

464. Cellular Mechanisms of Oscillations

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Support: Physician Sctientist Stipend of the Medical Faculty of the Heidelberg University

Title: Hippocampal fast-spiking interneurons are functionally more vulnerable to acute hypoxia-ischemia and reperfusion in comparison with pyramidal cells

Authors: *D. HEFTER, P. GRUBE, A. DRAGUHN, M. BOTH;
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Abstract: Fast-spiking interneurons (FSI) are considered to be more vulnerable to metabolic insults than pyramidal neurons (PYR) due to their high energy demand. As FSI orchestrate synchronous network activity such as gamma and sharp-wave ripple oscillations (SPW-R), impairment of their function following hypoxia-ischemia (HI) implies disturbed network function and excitatory-inhibitory balance, which may lay the basis for development of neuropsychiatric diseases. However, the acute effects of HI on FSI function and the consequences for network activity remain elusive. Therefore we employed a model of oxygen-glucose deprivation (OGD) and reperfusion in acute brain slices exhibiting spontaneous SPW-R and performed tetrode recordings from the hippocampal CA3 and CA1 regions. OGD was maintained until a hypoxic spreading depression occurred; then the tissue was allowed to recover for one hour under normoxic perfusion. Several spike sorting and clustering techniques were systematically tested to yield the optimal separation between putative FSI and PYR units. Despite potential tissue and cellular swelling during OGD, stable unit recordings were feasible throughout the experiment. Gaussian mixture models clustering based on the firing distribution

of the units (inter-spike intervals, bursting) yielded the best separation between FSI and PYR which appeared as clearly distinct clusters. Putative FSI showed an impaired functional recovery from OGD as compared to PYR (decreased firing frequency and bursting, reduced coupling to SPW-R). Furthermore, analysis of the functional connectivity revealed distinct changes in the inhibitory and excitatory connections between units. Following reperfusion, SPW-R recovered partially. Taken together, in this study we show increased functional impairment of putative FSI after OGD as compared to PYR. These findings are in support of the hypothesis that interneurons may be particularly severely affected following a metabolic insult which may cause an imbalance between excitation and inhibition.

Disclosures: D. Hefter: None. **P. Grube:** None. **A. Draguhn:** None. **M. Both:** None.

Poster

464. Cellular Mechanisms of Oscillations

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Topic: B.09. Network interactions

Support: European Research Council Grant ERC-2015-CoG 681577
German Research Foundation SFB 936 B5

Title: The development of pyramidal neurons - interneurons interactions in the mouse prefrontal cortex

Authors: *M. CHINI, I. L. HANGANU-OPATZ;
Univ. Med. Ctr. Hamburg-Eppendorf, Hamburg, Germany

Abstract: GABAergic interneurons are indispensable for the generation of different brain rhythms and the establishment of functional neuronal circuits. While their role in this regard has been subject to extensive research in the adult brain, little is known about their developmental contributions. Understanding how the embedment of interneurons into local circuits occurs is critical, as they are thought to be crucial for the generation of prefrontal beta/gamma rhythms related to cognitive processing, and their dysfunction has been reported for several neurodevelopmental disorders. To fill this knowledge gap, we used a combination of cre-lines and viral approaches to express inhibitory and excitatory light-sensitive opsins in a pan-interneuronal line (Gad^{2+}) and a line targeting interneurons derived from the medial ganglionic eminence ($Dlx5/6^{+}$). Combining *in vivo* extracellular recordings from the prelimbic subdivision of prefrontal cortex from non-anesthetized mice of 4-12 days of age with subtle and layer-specific optogenetic manipulations, we report that interneurons are critical mediators of early prefrontal oscillatory activity. Surprisingly, even at 4 days of age interneurons display adult-like characteristics and effects. They exert a strong inhibitory effect on the spiking of pyramidal

neurons and on local field potentials. As mice age, the quality of the effect does not change, but the magnitude, reliability, and dimensionality of the response robustly increase. Moreover, we used a variety of statistical methods to analyze more than 200.000 pairs of single unit spike trains and show that the blueprint of the functional architecture of the prefrontal cortex is already present in the first postnatal week. The maturation of inhibitory connectivity selectively shapes fast-scale synchrony between pairs of neurons, enhancing local and within-column connectivity, while pruning spurious and less specific connections. These data give first insight into the developmental mechanism of interneuronal wiring within prefrontal circuit.

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Poster

464. Cellular Mechanisms of Oscillations

Location: Hall A

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Topic: B.09. Network interactions

Support: ERC Grant 742595

Title: Specialized frontal cortical control over the anterior thalamic reticular nucleus

Authors: *N. HÁDINGER[1], E. BőSZ[1], G. VANTOMME[2], B. TÓTH[1], A. LÜTHI[3], L. ACSÁDY[4];
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Abstract: It has long been known that the neocortex is organized into areas with different cognitive functions. However, we are only beginning to understand the importance of regional specializations in cortico-thalamic interactions. Since basically all cortical functions involve cortico-thalamic communication, regional specialization of this loop according to the functional requirements is of high interest. In this study we describe a novel component in the cortico-thalamic pathway which is specific for the frontal cortices and innervates the thalamic reticular nucleus (TRN).
The entire TRN is under cortical control via inputs from the layer 6 (L6) of the neocortex. L5 cortical output, which otherwise exerts profound control over thalamic activity, was thought to reach thalamus without innervating TRN, mainly based on data from the sensory areas. In this study conditional viral tracing from the frontal but not parietal cortical areas in the L5-specific Rbp4-Cre mouse revealed dense, topographically-organized projection to the antero-ventral TRN. Compared to L6-TRN synapses the L5-TRN synapses showed distinct ultrastructural properties at the electron microscopic level. *In vitro* electrophysiological experiments

demonstrated that in contrast to the L6-TRN pathway the L5-TRN pathway displays short term depression instead of short term facilitation and that L5-TRN EPSCs has higher NMDA/AMPA ratio. Optogenetic activation of L5 cells in anesthetized mice elicited action potentials in anterior TRN with short latency and high fidelity. During spontaneous activity single spike activity of L5-recipient TRN cells showed low correlation with the ongoing frontal cortical oscillations, while high frequency longer TRN burst were tightly coupled with fast high amplitude cortical events indicating efficient control in case of cortical synchrony. Confirming this, optogenetically recruiting progressively more L5 cells converging on the TRN neurons resulted in TRN bursts with higher spike number and intra-burst frequencies. L5 driven TRN sectors innervated thalamic nuclei with frontal cortical connections. The data together suggest powerful and temporally precise cortical control specifically in frontal cortico-thalamic circuits via strong coupling of TRN cells to synchronized L5 outputs.

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Poster

464. Cellular Mechanisms of Oscillations

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Topic: B.09. Network interactions

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EIT Health Innovation by Ideas, NEURO-WEAR ProjectEIT Health Innovation by Ideas
Boateng Asamoah is SB PhD fellow at FWO

Title: Temporal dynamics of alternating current stimulation

Authors: *B. ASAMOAH[1], A. KHATOUN[1], M. MC LAUGHLIN[2];
[2]Neurosci., [1]KU Leuven, Leuven, Belgium

Abstract: Rationale
Neural spiking can phase lock to transcranial alternating current stimulation (tACS) provided the generated electric field in the brain is strong enough (transcranial mechanism). Recently we showed that there is also a transcutaneous mechanism where peripheral nerves are stimulated. They then give a rhythmic input to the brain. In tACS studies the stimulation duration is relatively long (~ 10 minutes). Supposedly, longer stimulation allows for more neuromodulation. This should then give a stronger behavioural effect. It is, nevertheless, not yet clear how neurons respond to these alternating currents (both transcranial and transcutaneous) over time.
Objective

We set out to understand this temporal aspect of the alternating current stimulation. Therefore we investigated the ongoing interaction between the neuron and the applied alternating current when the generated electric field is strong enough to affect neurons. We also investigated this interaction for the transcutaneous mechanism of tACS. Our main objective was to determine how long a decision maker would need to detect a change in neural entrainment caused by the stimulation. This is an important question as it is an indicator of the type of behavioural tasks which may be successful in humans.

Methods

In 7 anaesthetised male Wistar rats we opened the scalp and inserted a multichannel recording probe into the motor cortex via a craniotomy. We then recorded neural activity during 3 consecutive minutes. During the second minute of recording we also stimulated with a sinewave waveform. We stimulated either directly on the skull or on a limb. For the transcranial as well as transcutaneous condition we stimulated with 3 amplitude levels. This design allowed us to assess neural activity before, during and after stimulation. Also we were able to assess effects for different stimulation strengths.

Conclusions

Analysis shows that when stimulation (transcranial as well as transcutaneous) is turned on, neurons respond immediately. This response sustains over time and disappears rapidly when the stimulation is turned off.

We found that detection of neural entrainment effects at the neuron level depends on two factors: observation time and stimulation strength. Low stimulation levels produce entrainment effects which only become detectable over longer observation periods (tens of seconds). Higher stimulation levels produce entrainment effects that can be detected in shorter observation periods (seconds).

These results suggest that to observe behavioural neural entrainment effects in humans, tasks that rely on accumulation of information over longer periods of time are more likely to be successful.

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Poster

464. Cellular Mechanisms of Oscillations

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Support: BRAIN Initiative Grant U19 NS107464-01
Division of Intramural Research Program, NIMH

Title: Scale-invariant neuronal activity in primary visual cortex of awake mice

Authors: *E. CAPEK, D. PLENZ;
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Abstract: Brains must solve large information processing challenges in an efficient manner. It is well known that being in the critical regime can maximize certain computational capabilities of a network. Critical dynamics have been demonstrated in neural networks *in vivo*, suggesting that criticality may be a strategy brains adopt to improve their information processing efficiency. What is not known is to what extent different networks in the mammalian brain occupy this regime. In particular, it isn't known what cell subtypes and what layers of visual cortex participate in critical dynamics, and whether different visual stimuli can alter this participation. Here we study the scale-invariant aspects of neuronal activities as a proxy for critical network dynamics. We analyze the activity of select excitatory and inhibitory neuron populations in mouse visual cortex from a 2-photon imaging dataset made publicly available through the Allen Brain Observatory. We find specific aspects of scale-invariance in select groups of pyramidal neurons of V1 across a variety of stimulation patterns. Our results are in line with the idea that visual processing in V1 occurs at criticality.

Disclosures: E. Capek: None. **D. Plenz:** None.

Poster

464. Cellular Mechanisms of Oscillations

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Topic: B.09. Network interactions

Support: National Institutes of Health R01MH110311
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Title: Integrated information generated by cortico-striatal-thalamic circuits correlates with level of consciousness

Authors: *M. AFRASIABI[1], M. J. REDINBAUGH[1], N. A. KAMBI[1], J. M. PHILLIPS[1], S. MOHANTA[1], A. RAZ[2,4], A. M. HAUN[3], Y. B. SAALMANN[1];
[1]Psychology, [2]Anesthesiol., [3]Psychiatry, Univ. of Wisconsin-Madison, Madison, WI;
[4]Anesthesiol., Rambam Hlth. Care Campus, Haifa, Israel

Abstract: A prominent model of the neural correlates of consciousness (NCC: minimal brain mechanisms sufficient to produce conscious states), Integrated Information Theory, proposes that consciousness depends on integrated information (Φ), the information generated by a system above and beyond the information generated by its parts. Such integration must be supported by

reciprocal interactions between neural populations. While cortico-cortical and thalamo-cortical interactions are thought to contribute to the NCC, the basal ganglia are often disregarded. However, the thalamus provides often overlooked direct input to the striatum, allowing for thalamo-striatal interactions. To investigate the NCC status of cortico-striatal-thalamic circuits, we compared their integrated information across conscious states.
We used laminar probes to simultaneously record from the frontal eye field (FEF), lateral intraparietal area (LIP), caudate nucleus (CN) and central lateral thalamus (CL) in 2 macaques during general anesthesia (propofol or isoflurane) and wakefulness (resting state). Structural MRI of probes *in situ* verified positioning, and we identified cortical layers using current source density. To manipulate cortico-striatal dynamics and arousal, we electrically stimulated CL across 16 probe contacts (200 μA at 50 Hz). We analyzed data during stable eye epochs at baseline and with CL stimulation. To monitor consciousness level, we used EEG, EMG, eye position, and vitals. Recordings occurred in the dark with the animal's head stabilized.
We used a measure of integrated information based on cross-covariance of simultaneously recorded local field potentials (LFPs) over a short time window (200 ms). We compared the self-information I of a multi-channel system (mutual information across a time lag of 5 ms) with an estimate of the self-information I* of a *partitioned* version of the system, forcing independence of partitioned channels. The integrated information is the minimal difference of these quantities over all possible partitions ($\Phi^*=I-I^*$). We evaluated Φ^* for every subsystem of 6 cortical components (superficial, middle, deep layers of FEF and LIP) plus CN.
We found greater Φ^* during wakefulness versus (propofol and isoflurane) anesthesia. Moreover, Φ^* correlated with the increased level of arousal induced by electrically stimulating CL. During wakefulness the full cortico-striatal system had the largest Φ^*. Subsystems including the deep cortical layers tended to have higher Φ^*, especially those involving CN.
These results suggest that circuits involving not only cortical and thalamic components, but also striatal mechanisms, contribute to the NCC.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Collective activity of ventral CA1 neuronal populations in awake mice

Authors: *U. CHOCKANATHAN, E. WARNER, K. PADMANABHAN;
Neurosci., Univ. of Rochester, Rochester, NY

Abstract: The ventral CA1 (vCA1) region of hippocampus is implicated in an array of behaviors including spatial navigation and memory, anxiety, social recognition, and social memory. This constellation of behaviors arises from the unique connectivity of vCA1, which includes afferents from entorhinal cortex, amygdala, and piriform cortex and efferents to nucleus accumbens, prefrontal cortex, and main olfactory bulb. Furthermore, within vCA1, molecular, cellular, and biophysical diversity influence the heterogeneity in neural responses and their links to behavior. While each of these features, and the single-neuron responses associated with them, has been extensively studied, the manner in which vCA1 neurons collectively participate in guiding behavior remains largely unknown. Importantly, the structure of vCA1 population activity, the implications of this activity for neural coding, and the ways in which this activity is disrupted in diseases is not well understood. To address this, we made extracellular recordings from large populations of neurons in vCA1 in awake mice running on a linear wheel in a virtual reality environment by stereotactically targeting a 128-channel silicon electrode array to vCA1 (coordinates relative to bregma: -3.15mm AP, 3.25mm ML, 4.00mm DV). To understand this activity, we calculated the entropy, a measure of the diversity of network states, of ensembles of neurons (N = 3-40 neuron subpopulations) in two states: while the animal was running and while it remained stationary. Next, to understand the organizational principles of the population, including the functional coupling between neurons, we fit the population activity to a class of maximum entropy models derived from statistical physics. These models capture the global structure of activity using a minimal set of assumptions, such as the probability of firing of individual neurons and the functional coupling between pairs of neurons. We compared the predicted network states from the model with that of the recorded population to understand how individual firing rates and pairwise interactions govern overall population states. Finally, we considered the role that higher order interactions between neurons (triplet and quadruplet interactions, for instance) play in governing the activity of vCA1 networks. This study will determine how vCA1 neurons function collectively to drive network activity.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Dendritic properties of parvalbumin interneurons enhance robustness of gamma oscillations

Authors: *K. VERVAEKE, H. HU, B. KRIENER;
Univ. of Oslo, Oslo, Norway

Abstract: Network oscillations in the gamma range (40-100 Hz) are important for many cognitive tasks by coordinating the temporal organization of neural ensembles. Parvalbumin (PV)-expressing inhibitory neurons that form reciprocal synaptic connections tend to fire action potentials at gamma frequencies, suggesting an important role in generating gamma oscillations. However, the circuit mechanisms underlying gamma rhythms remain poorly understood. A consistent problem of inhibitory network models is that synchrony is not robust against heterogeneities in the excitatory synaptic drive. Fast and strong inhibitory synapses and shunting inhibition increase robustness, but when exposed to biologically realistic heterogeneities, network synchrony in these models still fails. Classic work performed network simulations using 'point-neuron' models that lump the morphology of cells into a single compartment. Here, however, we hypothesized that the dendritic morphology of PV neurons could be essential to generate robust gamma rhythms. Using dual patch clamp recordings of the soma and dendrites of PV neurons in the dentate gyrus, we show that the slope, or gain, of the input-output relationship is much lower for dendritic input compared to somatic input. Thus the dendrites scale down the sensitivity of a PV neuron to changes in its input. This is due to the unique properties of PV neuron dendrites that express a high density of K^+ channels and a low density of Na^+ channels. Using biologically realistic network models composed of PV cells with reconstructed dendrites, we tested how their dendritic properties affect network synchrony. We found that the low gain of the input-output relationship homogenizes the firing rates of cells in the network, thereby not only allowing much higher input heterogeneities, but also relaxing the requirement for strong inhibitory coupling. This demonstrates that the unique properties of PV neuron dendrites are essential to produce gamma oscillations and support the many cognitive tasks correlated with this brain rhythm.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Variability in response to electrical stimulation changes with brain state in humans

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Abstract: Since sleep or loss of consciousness has long been known to alter underlying brain dynamics, the human brain's response to electrical stimulation likely also change in these altered brain states. We investigate the variability of the response to single-pulse direct electrical stimulation (SPES) in the intracranial EEG (sEEG) while participants are awake, asleep, or under anesthesia.

Working with patients with pharmaco-resistant complex partial seizures implanted for clinical reasons who voluntarily participated after fully informed consent (N=4), we performed SPES (pulse: 7uA, inter-stimulation interval 2+/-0.25s) across 5 brain regions during wake and anesthesia. In a subset, we repeated the experiment during sleep (N=2). We analyzed 20 (or 12 during sleep) bipolar pairs of intracranial channels near stimulation electrodes with cortico-cortical evoke potentials (CCEP) responses to stimulation during wake. Up to 15 SPES pulses were selected per state per channel, resulting in 300 total events (sleep: 149) for analysis. We compared CCEP between wake in the epilepsy monitoring unit (wakeEMU), sleep, wake in the operating room before anesthesia induction (wakeOR), and anesthesia. We found increased variability in CCEPs peak time and amplitude during sleep and anesthesia in individual bipolar pairs. To quantify this observation, we selected three intervals corresponding to CCEP peaks (N1: 5-50ms; N2: 50-200ms; Long: 200-1000ms) and computed the standard deviation (STD) of the absolute response amplitude. Paired t-tests of log10(STD) between states were performed. The mean variability across channels was higher during anesthesia and sleep than for wake (EMU & OR) for N1, N2 and Long intervals. We found significant differences ($p<0.01$) between wake and anesthesia for N1 and Long intervals. Importantly, similar results were obtained when normalizing by the baseline variability at each state.

We then asked if peak-time and amplitude of the largest peak for each interval changed during each state, defined as the maximum absolute amplitude of the sEEG z-score normalized to baseline (30s before first stimulation). We found that peak amplitudes during the anesthesia state were smaller for all intervals. Significant differences ($p<0.05$) were found between wakeEMU and sleep for all intervals and between wake (EMU & OR) and anesthesia for N1 and N2 intervals. For peak-time, significant differences ($p<0.05$) were found between wake and anesthesia for N2 and long intervals.

Our results suggest an increase in variability in the response to stimulation when consciousness is lost, paving the way for a potential new electrographic biomarker of consciousness.

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Purdon: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on patents pending on brain monitoring technologies assigned to Massachusetts General Hospital, Inventor on a patent assigned to Massachusetts General Hospital and licensed non-exclusively to Masimo Corporation. Other; Co-Founder of PASCALL Systems, Inc., a start-up company developing closed-loop physiological control systems. **S.S. Cash:** None.

Poster

464. Cellular Mechanisms of Oscillations

Location: Hall A

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Title: Functional disruption of intracranial EEG dynamics during subanesthetic ketamine-induced dissociative state

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Abstract: Ketamine is a widely used anesthetic. At higher doses, ketamine induces unconsciousness and immobility, whereas at lower or subanesthetic doses, it produces a dissociative state, which includes altered sensory perception and a sense of disembodiment. The mechanism whereby subanesthetic doses of ketamine disrupts functional brain activity to produce the dissociated state remains unclear. The objective of this study is to investigate in humans the effects of subanesthetic doses of ketamine on brain dynamics and the dissociative state.

Five epilepsy patients were implanted with intracranial depth, surface, and strip electrodes for detection of seizure foci. We recorded during a ketamine infusion administered just prior to the electrode removal surgery. Baseline signals were recorded for 5 minutes. Then each patient

received an infusion of a subanesthetic dose of ketamine (0.5 mg/kg over 14 minutes). During ketamine administration, the patients performed an auditory task consisting of interleaved verbal and click stimuli presented every 3.5-4.5 seconds. Patients completed an abbreviated version of the Clinician-Administered Dissociative States Scale (CADSS) questionnaire at the conclusion of the ketamine infusion.

The responses on the CADSS questionnaire and the intermittent responses to the auditory stimuli confirmed that our subanesthetic ketamine administration paradigm induced a dissociative state. This state was associated with decreased of alpha oscillation power in precentral gyrus, similar to a prior report showing that subanesthetic doses of ketamine induces a dissociative state by disrupting multisensory integration in the precuneus and temporal-parietal junction that are modulated by alpha waves. Patients also exhibited an increase of gamma oscillation power in both frontal and temporal lobes under subanesthetic ketamine. Additionally, global coherence analysis demonstrated that administration of a subanesthetic ketamine dose leads to the onset of broadband low gamma/high beta coherence. Finally, phase amplitude coupling between slow (0.1-1Hz) and beta oscillations displayed a transition from coupling in which beta oscillations are larger in the troughs of the slow oscillation ("trough-max") at baseline, to another form of coupling in which beta is largest at the peaks of the slow oscillation ("peak-max") after the ketamine infusion. Collectively, these findings indicate that disruption of the dynamic coordination between brain regions may play an important role in mediating the ketamine-induced dissociative state.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Slow oscillatory activity across neocortex and hippocampus is at least partially coordinated by the thalamic nucleus reuniens

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Abstract: Synchronized activity across the brain is a hallmark of sleep, a phenomenon which has physiological relevance for a host of functions. In particular, coordinated activity between medial prefrontal cortex (mPFC) and hippocampus (HPC) has been suggested to be critical for some mnemonic processes during both wakefulness and sleep. One of the most ubiquitous and physiologically relevant activity patterns occurs during slow-wave states, a ~1 Hz rhythm known as the slow oscillation (SO). However, it is currently unclear how the SO is coordinated between mPFC and HPC. Here, we examined the nucleus reuniens (RE), a midline thalamic body with direct, reciprocal projections to both mPFC and HPC, for its possible role in synchronizing the SO between these disparate sites. We used a rat model under urethane anesthesia because of how closely and dynamically it models natural sleep, in terms of alternations of forebrain state and corresponding physiological measures. We first characterized RE neuronal activity using single- and multi-unit recordings, determining that RE units rhythmically fire during, and are phase synchronized with, the mPFC SO. Optogenetic excitation of the RE reliably produced an evoked response in the HPC. Similarly, exciting the mPFC produced a similar evoked response in the HPC, with longer latency. Chemogenetically inhibiting the RE blocked this mPFC-mediated evoked potential in the HPC, suggesting that the RE is a critical and functional excitatory intermediary between mPFC and HPC. Importantly, during RE inactivation, we observed a robust decrement in mPFC-HPC coherence at SO frequencies. Critically, this diminished synchrony was not a consequence of decreased SO power, which was unchanged pre- and post-RE inhibition. Our results demonstrate a decisive role for the RE in at least partly mediating mPFC-HPC SO coordination, a phenomenon which has marked implications for sleep-dependent memory consolidation.

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Poster

464. Cellular Mechanisms of Oscillations

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Department of Anesthesia, Critical Care and Pain Medicine, MGH, Boston, MA (to F.J.F., P.L.P., E.N.B.)

Title: Differences in thalamocortical synchronization during sleep and anesthesia-induced unconsciousness

Authors: *J. B. BRISCOE[1,2], J. HARROD[2], M. A. WILSON[2], P. L. PURDON[1], E. N. BROWN[1,2], F. J. FLORES[1,2];
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Abstract: Drug-induced unconsciousness, as observed during general anesthesia, is characterized by cortical activity exhibiting high amplitude, low frequency oscillations. The physiological state of unconsciousness observed during sleep displays a similar pattern of cortical activity, but it is fundamentally different from the unconsciousness observed during anesthesia. During sleep, the subjects can easily wake up in response to mild-intensity sensory stimuli, while during anesthesia the subjects are unresponsive even in the presence of severe tissue damage. We have previously shown, by simultaneously recording extracellular activity in frontal cortex and anterior thalamus, that the unconscious state induced by propofol dosing is characterized by frontal thalamocortical synchronization in both delta (1-4 Hz) and spindle/alpha (10-15 Hz) frequency bands. We wondered if the stark differences in responsiveness between sleep and anesthetic-induced unconsciousness is due to differences in the degree of thalamocortical synchronization. We implanted male Sprague-Dawley rats, weighing 500 to 700 g, with silicon probes aimed at prefrontal cortex and anterior thalamus, and recorded cortical and behavioral activity while the animals were allowed to freely behave in a box. To identify the periods of wakefulness and non-REM sleep, we fed the electrophysiological and behavioral recordings into a deep belief artificial neural network, consisting of a linear classifier on the top and a structure of 100 x 100 hidden layers based on restricted Boltzmann machines. We observed

that while the power of cortical and thalamic signals in the delta and spindle/alpha bands increases during non-REM sleep, the thalamocortical coherence observed during non-REM sleep it is not significantly different from the thalamocortical coherence observed during wakefulness. However, different classes of anesthetic drugs produce an increased level of thalamocortical coherence in the delta and alpha frequency bands. The lack of sustained frontal thalamocortical coherence during non-REM sleep may provide a plausible mechanism to explain the stark difference between sensitivity to external stimuli observed during sleep-related unconsciousness and anesthetic-induced unconsciousness.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: A tale of two alpha oscillations: Spatially coherent alpha dynamics during propofol-induced unconsciousness reflect functional organization of thalamocortical connections

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Abstract: Propofol-induced anesthesia produces reproducible oscillatory dynamics that can be recorded at the scalp: the loss of posterior sensory alpha (~10 Hz) rhythms and rise of coherent anterior alpha rhythms. Thalamocortical circuits are thought to underlie both alpha rhythms; however, the spatiotemporal and functional properties of alpha networks and the roles of thalamic nuclei in organizing them are not fully deciphered. We hypothesized that regional cortical alpha dynamics would reflect specific connectivity patterns to thalamic nuclei. We studied neurophysiological recordings from 11 patients with intracranial depth and electrocorticography (ECoG) electrodes as they received propofol general anesthesia while performing a behavioral task. Using multitaper spectral and global coherence analyses to track spatiotemporal dynamics of alpha, we estimated each channel's contribution to alpha coherence before and after loss of consciousness (LOC). We then selected two subsets of the channels with the greatest increase and decrease in alpha coherence, respectively. For each patient, we found 3 matched surrogates from the Human Connectome Project WU-Minn diffusion-weighted imaging dataset and performed probabilistic tractography from regions of interest representing the two channel groups to individual thalamic nuclei using a probabilistic atlas. Finally, we mapped both channel groups to their corresponding resting-state functional networks, using the Yeo atlas. After LOC, alpha coherence showed the strongest decrease in the visual, auditory and somatosensory cortices and the strongest increase in the anterior cingulate, orbitofrontal cortex, and medial temporal lobe. These two alpha networks are associated with connections to distinct thalamic nuclei. First, the posterior sensory cortices showing the greatest decreases in alpha power after LOC are connected to the pulvinar and ventral posterolateral nuclei. The frontal and midline structures showing increased alpha rhythms after LOC are connected to the mediodorsal and ventral anterior nuclei. These results suggest that loss of posterior (sensory) alpha is associated with impairment of processing of external stimuli, whereas alpha coherence in the frontal regions, belonging to the ventral attention functional network, would impair self-awareness and internal consciousness and impede responsiveness to external stimuli.

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Poster

464. Cellular Mechanisms of Oscillations

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Topic: B.09. Network interactions

Support: NSERC 2016-06576
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Title: Identifying convergent components of unconscious brain state dynamics in sleep and anesthesia

Authors: *R. WARD-FLANAGAN, A. LO, M. SOBEY, C. T. DICKSON;
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Abstract: The unconscious state produced by natural sleep is unique and dichotomous. It consists of spontaneous, cyclical alternations between an activated state known as rapid-eye movement (REM; characterized by low-voltage, fast EEG activity) and deactivated state known as non-REM (NREM; characterized by large amplitude, slow oscillatory activity). These physiologically discrete states and the recurring fluctuations between them have made it difficult to model the complete neurophysiological spectrum of natural sleep without using sleep itself. Our aim in the current study is to characterize how select common anesthetics promote specific electrophysiological components of natural sleep in order to find a reliable pharmacological proxy for natural sleep.
We assessed a number of commonly used anesthetics as potential candidates for a pharmacological model of sleep, including isoflurane, ketamine-xylazine, pentobarbital, chloral hydrate, and propofol. Sprague-Dawley rats were randomly assigned to one of the anesthetic groups for acute electrophysiological recordings in the cortex and hippocampus. All anesthetics were delivered intravenously, except isoflurane which was delivered continuously via nosecone. Dosage was consistently monitored and adjusted to maintain a surgical plane of anesthesia.
At a surgical plane, electrophysiological activity in rats in the ketamine-xylazine, and chloral hydrate anesthesia groups exhibited a unitary state of large amplitude, slow oscillatory activity resembling NREM sleep. In the isoflurane, pentobarbital, and propofol anesthesia groups we observed a burst-suppression pattern of activity, which is consistent with the electrophysiological activity archetypically observed in a coma state. Interestingly, rats in the urethane anesthesia group exhibited an pattern of activity with cyclic and spontaneous alternations between an activated state of low-voltage fast cortical activity concomitant with theta (~ 4 Hz) in the hippocampus, and a deactivated state of large-amplitude, slow oscillations (~ 1 Hz) in both the

cortex and hippocampus. These changes in brain state corresponded with modulation of physiological functions, including respiratory activity, heart rate, and temperature, which are all typically observed in natural sleep during transitions between REM and NREM. Subsequently, our data suggests that only urethane anesthesia exhibits the full neurophysiological spectrum of natural sleep in terms of components, dynamics and time frame. Consequently, urethane is the most viable pharmacological proxy for the spontaneous cyclic alternations of sleep that we have assessed at present.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Phase coupling versus amplitude coupling; two associated but distinct modes of neural connectivity

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Abstract: While communication across distant neural populations is critical for all cognitive processes, researchers use fundamentally different measures to assess such functional connectivity (FC). Some neurophysiological studies use phase coupling (*PhC*) defined as coupling between the phases of two signals, reflecting the synchronization of rhythmic oscillation cycles. Others use amplitude coupling (*AmpC*) defined as coupling between the envelopes of two signals, reflecting synchronization of activation amplitude. PhC and AmpC thus quantify different neurobiological mechanisms, yet the relationship of the two remains elusive. In addition, task-based studies of neurophysiological data commonly use PhC, while AmpC has been mostly used for resting state data. Therefore, investigating correspondence between PhC and AmpC not only clarifies to what extent and how these two neural mechanisms relate to each other, but also provides an informative link between findings of task-based and resting state studies. We assessed spatial and temporal correspondence between PhC (measured by Phase Locking Value) and AmpC over 5 canonical frequency bands using intracranial Electrocorticography (ECoG) in 10 patients undergoing presurgical evaluation. In each

frequency band, spatial correspondence was estimated as correlation across the static FC matrices of PhC and AmpC. Subsequently, temporal correspondence in each frequency band was evaluated using temporal correlations between PhC and AmpC dynamics for each electrode pair. Significant correspondence between the spatial pattern of PhC and AmpC was detected during stimulus processing in all subjects and all frequency bands ($R \approx 0.48$ for delta, progressively decreasing with increasing frequency). This spatial correlation vanished almost entirely ($|R| < 0.07$) when accounting for FC already present prior to stimulus onset, suggesting that the spatial correlations reflected intrinsic FC independent of stimulus processing. Regarding the temporal relationship between PhC and AmpC dynamics, we not only observed a considerable proportion of connections with positive correlations across the dynamics (~28%), but also substantial proportions of connections with anti-correlated (~24%) or uncorrelated dynamics (~48%). We conclude that PhC and AmpC reflect intrinsic FC in a similar fashion across space, while they expose both interrelated and divergent stimulus-related FC changes across time. Consequently, PhC and AmpC constitute two distinct but associated modes of neural communication.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Dynamical evolution of spatiotemporal patterns of cortical activity under different brain states

Authors: *A. CAMASSA[1], M. DASILVA[1], M. MATTIA[2], M. V. SANCHEZ-VIVES[1,3]; [1]IDIBAPS (Institut D'Investigacions Biomediques August Pi I Sunyer), Barcelona, Spain; [2]Inst. Superiore di Sanità, Roma, Italy; [3]ICREA, Barcelona, Spain

Abstract: Conscious and unconscious states are associated with specific characteristics based on the spatiotemporal dynamics of ongoing brain activity. In this study we aimed to characterize different brain states by studying the changes occurring to the spatiotemporal dynamics of slow-wave propagation in multichannel cortical data. During the sleep-like slow oscillations (SO, < 1Hz) regime, activation waves spontaneously emerge and propagate across the cortical network both *in vitro* and *in vivo* in anesthetized animals (Sanchez-Vives and McCormick, Nat Neurosci., 2000; Ruiz-Mejias et al., J Neurophysiol., 2011). Here, we varied the brain states *in vivo* by

varying the anesthesia levels, without departing from the slow-wave activity regime: the emergent oscillatory activity ranged from lower (0.12 Hz) to higher (1.15 Hz) frequency for high to low anesthesia levels respectively. We recorded the extracellular local field potential (LFP) with a superficial 32-channel electrode-array placed on the surface of the brain of eight mice anesthetized at three different levels and developed a phase-based method to reconstruct the spatiotemporal dynamics of propagating waves in multichannel recordings. The instantaneous phase at each electrode and the latency were computed as in Muller et al., Nat. Commun., 2014. As a result, we were able to define the patterns of propagating activity under each anesthesia level, to study their dynamical evolution over time, and estimate for each brain state the overall dynamical richness and sequence predictability. Overall, our findings allowed us to characterize the evolution of the cortical dynamics under different brain states within the SO regime, revealing that the wave propagation patterns change together with the brain state showing richer spatiotemporal dynamics in lighter anesthesia states, supporting the idea of an increasingly complex brain activity that varies when we move from deeply unconscious states towards wakefulness.

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Poster

464. Cellular Mechanisms of Oscillations

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Title: Physiology of broadband high-frequency activity: Evidence from intracortical laminar recordings in human and nonhuman primates

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Abstract: Broadband High-frequency Activity (BHA; 70-150 Hz), also known as "high gamma," a key analytic signal in human intracranial recordings is often assumed to reflect local neural firing (multiunit activity; MUA). Accordingly, BHA has been used to study neuronal population responses in auditory, visual, language, mnemonic processes and cognitive control. BHA is the electrophysiological measure best correlated with the Blood Oxygenation Level Dependent (BOLD) signal in fMRI. Although critical for interpreting intracranial signals in human and non-human primates, the neuronal populations and physiological processes generating BHA remain unknown. Here, we show that BHA dissociates from MUA in primary visual (2 monkeys) and auditory cortex (2 monkeys). Using laminar multi-electrode data, we found a bimodal distribution of stimulus-evoked BHA across depth of a cortical column: an early-deep, followed by a later-superficial layer response. Only the early-deep layer BHA had a clear local MUA correlate, while the more prominent superficial layer BHA had a weak or undetectable MUA correlate. In many cases, particularly in V1 (70%), supragranular sites showed strong BHA in lieu of any detectable increase in MUA. Due to volume conduction, BHA from both the early-deep and the later-supragranular generators contribute to the field potential at the pial surface, though the contribution may be weighted towards the late-supragranular BHA. Our results demonstrate that the strongest generators of BHA are in the superficial cortical layers and show that the origins of BHA include a mixture of the neuronal action potential firing and dendritic processes separable from this firing. It is likely that the typically-recorded BHA signal emphasizes the latter processes to a greater extent than previously recognized. The ongoing work aims to test whether these dissociations are also observed during active visual exploration.

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Poster

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Title: Excitatory and inhibitory regulation of cortical network complexity

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Abstract: The cortical network is composed of thousands of units interacting in different ways throughout different brain states, resulting in a variety of cortical dynamic patterns. From the awake state to deep sleep, anesthesia or coma states, there are profound changes in cortical interactions both in the temporal and the spatial domains. As a result, the awake state is characterized by complex patterns of causal interactions, whereas this complexity collapses in deep sleep or anesthesia. An understanding of the mechanisms that enable the emergence of complex brain states is critical for the development of reliable monitors of brain state transitions and of consciousness levels during anesthesia and in brain-injured patients, and for devising mechanistically-based interventions to promote state transitions and recovery of function. To this end, in a previous study we adapted a measure of cortical complexity, the perturbational complexity index, originally devised for human EEG (Casali et al., *Sci Trans Medicine* 2013), to the *in vitro* cortical network (D'Andola et al, *Cerebral Cortex*, 2017). We demonstrated that complexity was low during slow oscillations, and increased in awake-like states induced by cholinergic and noradrenergic agonists. In the current study, we explore the role of $GABA_A$ and $GABA_B$ inhibition on the modulation of cortical spatiotemporal complexity during both synchronous (slow oscillations) and asynchronous (awake-like) regimes while recording from the surface of the slice with 16-channel multielectrode arrays. Our experiments demonstrate that progressively blocking either fast or slow inhibition decreases complexity, even when network excitability increases. This illustrates that complexity varies independently of excitability as we have previously found while varying excitability by means of electric fields (Barbero-Castillo et al., *Brain Stimulation*, 2019). Our results demonstrate that an orchestrated participation of excitatory and inhibitory components is required for the maintenance of cortical complexity.
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Disclosures: A. Barbero-Castillo: None. **P. Mateos-Aparicio:** None. **L. Perez-Mendez:** None. **S. Caldas-Martinez:** None. **M.V. Sanchez-Vives:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.01/B88

Topic: B.09. Network interactions

Title: Differential roles of three distinct pyramidal cell subpopulations during ongoing gamma oscillation in mouse hippocampal area CA3 *in vitro*

Authors: *H. BALLEZA-TAPIA, A. FISAHN;
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Abstract: Gamma oscillations in hippocampus emerge from the synchronous firing of action potentials (AP) of different neuronal classes as a result of the coordinated interaction between excitation and inhibition in a neural network. In the past years, a few studies have described distinct pyramidal cell (PC) subpopulations in hippocampal area CA3 with differing electrophysiological and morphological properties. However, the role of each PC subpopulation for CA3 neural network function is poorly studied.
By performing whole-cell patch-clamp recordings in mouse hippocampal slices we described 3 electrophysiological distinct subtypes of PCs in area CA3 with a specific anatomical distribution within the stratum pyramidale (s.p.). We found that PCs located close to the edge of s.p. and stratum oriens displayed a burst-like firing pattern (BF-PCs) of APs. In contrast, PCs located within the s.p. could be divided according to their AP adaptation rates into strong adapters (A-PCs) and weak- or non-adapters (WA-PCs).
To study the involvement of PC subpopulations during the initial- and stable-phase of gamma oscillations we performed simultaneous patch-clamp and local field potential (LFP) recordings in hippocampal slices activated with kainate. We found that while A- and WA-PCs firing was involved both in the initial- and stable-phase, BF-PCs did not participate in gamma oscillations since none or few APs were fired.
We also studied the excitatory/inhibitory input to PCs by recording the EPSCs and IPSCs. We found that EPSC frequency of A-PCs was higher than in WA- and BF-PCs only during the initial-phase of gamma oscillations. EPSC amplitude of A-PCs was higher than in BF-PCs only in the stable-phase. Compared to BF-PCs, IPSC amplitude of both A- and WA-PCs was higher in the initial- and stable-phase of gamma oscillations. IPSC frequency of WA-PCs was higher than in A- and BF-PCs only in the initial-phase.
Finally, to further evaluate the relationship between gamma oscillations and the excitatory/inhibitory input to PCs we calculated the cross-correlation between the whole-cell and LFP signals and found that EPSC-LFP cross-correlation peak (XC-Peak) and lag (XC-Lag) were similar between the 3 PC subpopulations. In contrast, IPSC-LFP XC-Peak of A- and WA-PCs was significantly higher compared to BF-PCs in both the initial- and stable-phase of gamma oscillations. XC-Lag of WA was higher than BF-PCs only in the stable-phase. In conclusion, our data support the hypothesis that CA3 PCs are organized into distinct subpopulations with differential roles in cognition-relevant neuronal network dynamics and provide new insights in the physiology of the hippocampal circuitry.

Disclosures: H. Balleza-Tapia: None. **A. Fisahn:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.02/B89

Topic: B.09. Network interactions

Support: MINECO Grant BFU2015-66887-R
MECD Grant FPU2017
MICINN Grant RTI2018-098581-B-I00

Title: Factors determining theta phase preference across CA1 sublayers

Authors: *A. NAVAS-OLIVE[1], M. VALERO[2], A. DE SALAS-QUIROGA[3], T. JURADO-PARRAS[1], E. CID[1], L. M. DE LA PRIDA[1];
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Abstract: Hippocampal pyramidal cells fire selectively to build abstract representations of a contingency of visual, auditory, somatosensory and behavioural events. While moving around these “spaces”, sequences of hippocampal “place cells” are activated in an orderly manner coordinated by the theta rhythm (4-12 Hz). One mechanism determining these sequences is theta phase precession, which occurs anytime the animal traverses a “place field”. However, hippocampal cells also exhibit a specific phase preference, which can be influenced by the global brain state. Here, we aim to study factors underlying theta phase preference across deep and superficial CA1 pyramidal sublayers during theta oscillations. First, we obtained juxtacellular and multi-site recordings in awake head-fixed mice and freely-moving rats. We found a characteristic bimodality in the distribution of the preferred firing phases of CA1 pyramidal cells. In order to understand the underlying factors, we built a biophysically realistic model that includes most of the known excitatory and inhibitory inputs converging in deep and superficial cells. The sublayer location was one factor explaining firing bimodality, but we found other influencing axes as well such as entorhinal and intra-hippocampal inputs. We tested some of the model predictions using cell-type specific chemogenetic approaches and unsupervised dynamical analysis of LFP activity. We discuss on the multiple dimensions determining phase preference and speculate about their potential role in defining episodic memory function.

Disclosures: **A. Navas-Olive:** None. **M. Valero:** None. **A. de Salas-Quiroga:** None. **T. Jurado-Parras:** None. **E. Cid:** None. **L.M. De La Prida:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: B.09. Network interactions

Support: MAFAT
Rosetrees Trust
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Jack H. Skirball Chair & Research Fund in Brain Research
Goren-Khazzam scholarship

Title: Phase-specific intra-cortical microstimulation in a brain-machine interface environment differentially modulates beta oscillations in motor cortex and affects behavior

Authors: *O. PELES[1,2], U. WERNER-REISS[1,2], H. BERGMAN[1,2], Z. ISRAEL[3], E. VAADIA[1,2];
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Abstract: It is widely accepted that oscillatory activity in the beta-band, prevalent in the motor cortex, plays a major role in complex tasks such as planning and execution of sensorimotor behavior. Thus, being able to modulate these neuronal patterns in behaving animals may impact our understanding of cortical dynamics. In order to experimentally manipulate oscillations, we trained monkeys, implanted with arrays of 96 electrodes in the motor cortex, to volitionally enhance local field potential (LFP) beta-band (20-30Hz) activity at selected sites by neural operant conditioning, using a real time brain machine interface (BMI) environment. Subsequently, we applied intra-cortical microstimulation (ICMS), precisely timed to oscillation phases.
We demonstrate that beta oscillations of LFP and single-unit spiking activity increased dramatically following the BMI training, and that pre-movement beta-power was positively correlated with the reaction times, and negatively correlated with task success rate. Furthermore, we show that phase-specific ICMS modulated the power and phase of the oscillations, shifting local networks between oscillatory and non-oscillatory states. Lastly, these stimuli induced phase-dependent effects on the animal's behavior.
Our findings may contribute to unraveling the functional role of cortical oscillations. In addition, this research can pave the way for the use of an advanced BMI platform for a wide range of neurological and psychiatric disorders where volitional control (biofeedback) aided by fine-tuned electrical stimulations can restore normal activity whenever abnormal patterns are identified.

Disclosures: **O. Peles:** None. **U. Werner-Reiss:** None. **H. Bergman:** None. **Z. Israel:** None. **E. Vaadia:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.04/B91

Topic: B.09. Network interactions

Support: Sir Henry Wellcome Postdoctoral Fellowship (209120/Z/17/Z)
Medical Research Council, UK (MC_UU_12024/1)

Title: Phase-dependent closed-loop modulation of neuronal oscillations

Authors: ***C. G. MCNAMARA**, M. ROTHWELL, A. SHAROTT;
MRC Brain Network Dynamics Unit, Dept. of Pharmacol., Univ. of Oxford, Oxford, United Kingdom

Abstract: Closed-loop modulation, whereby features of ongoing brain signals are used to control the timing of electrical or optical stimulation, has the potential to provide targeted manipulation of functional and dysfunctional neuronal activity. Field potential oscillations provide an attractive input signal for such modulation, providing a robust signal to inform the timing of stimulation. Normal brain function is associated with an assortment of oscillations of various frequencies having different properties across brain networks, each reflecting the timing of separate computational processes and levels of synchronization between and within associated brain areas. As such, stimulation accurately delivered on a specified phase of a given oscillation provides the opportunity to target individual aspects of brain function. To this end, we have developed a highly responsive closed-loop system using a digital circuit to produce a continuous online phase-estimate. In addition to stable oscillations, the system is capable of tracking the early cycles of short, transient oscillations across the full described frequency range (from 4 to 250 Hz and above). The system is implemented as a hardware description in Verilog and can be added to any recording system where electrophysiology data is routed through an FPGA, making it widely applicable. We deployed the system on an Intan USB interface board and used it to test the effect of phase-dependent closed-loop stimulation using two experimental setups. Firstly, we used behaving, parkinsonian rats that had received a 6-OHDA hemi-lesion to the substantia nigra pars compacta producing robust high-beta frequency oscillations (28 - 40 Hz) across the cortex and basal ganglia. A phase-estimate was calculated from an electrocorticogram above motor cortex to control the timing of pulsatile electrical stimulation of basal ganglia nuclei. Within individual animals, target phases that led to amplification and suppression showed different stimulation delivery characteristics suggesting stimulation worked in a truly closed-loop manner. Secondly, we drove optogenetic stimulation of the motor thalamus based on the phase of

different oscillation frequencies recorded from the reciprocally-connected motor cortex. These experiments demonstrate that both electrical and optical closed-loop phase-dependent stimulation can be used to modulate transient oscillatory activity across forebrain networks. Such approaches could provide a powerful tool for modulating neuronal oscillations associated with brain disorders and investigating the functional role of various rhythmic activities in normal brain function.

Disclosures: C.G. McNamara: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent pending. **M. Rothwell:** None. **A. Sharott:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent pending.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.05/B92

Topic: B.09. Network interactions

Title: Ketamine-induced impairment in hippocampal network gamma oscillation: Reversal by the mGlu2/3 receptor agonist LY379268

Authors: *T. GAO, H. CRUCES_SOLIS, H. ROSENBROCK, N. SCHUELERT;
CNS Dis. Res., Boehringer Ingelheim Pharma GmbH & Co. KG, Bibrach an der Riss, Germany

Abstract: Cognitive deficits are a core feature of schizophrenia. Network gamma oscillations (20-80 Hz) in prefrontal cortex and hippocampus are crucial for healthy cognitive function. In schizophrenia patients, as well as in animal models related to schizophrenia, abnormal gamma oscillations has been observed correlating with impaired cognitive function. Glutamate hypothesis of schizophrenia suggested that NMDA receptors in GABAergic interneurons are hypofunctional resulting in disinhibition of the glutamatergic efferent neurons and hence increased glutamate release and gamma oscillations indicative of excitatory/inhibitory (E/I) imbalance. Activation of metabotropic glutamate receptor 2/3 (mGluR2/3) by its agonist LY379268 suppresses presynaptic glutamate release and further, reversed the impairment of PCP-induced attention [1] and ketamine-induced increase of gamma oscillations [2]. In present study, we used mouse hippocampal slices to evaluate the effect of LY379268 on pharmacologically induced gamma oscillations in CA3 region. Local filed potential were recorded in CA3 region of acute hippocampal slices from 6-8 weeks old male C57BL6/J mice. Induction of gamma oscillations were produced by either 20 µM carbachol or 150 nM kainate. Then, we used 10 µM ketamine, a non-competitive NMDA receptor antagonist, to induce an E/I imbalance, and LY379268 was co-infused to evaluate effects on leading frequency and total

power of the 20-80 Hz gamma band. After induction of gamma oscillations by carbachol or kainate, the leading frequencies in ketamine-infused hippocampal slices were significantly lower compared to control slices. Co-infusion with LY379268 reversed the ketamine-induced alteration of gamma oscillation. We conclude that ketamine can change the network gamma oscillation in hippocampus and its effect can be reversed by co-administration of the mGlu2/3 agonist LY379268. These results provided new in-vitro evidence corroborating previous findings that mGluR2/3 might be a potential therapeutic target for cognitive deficits related to schizophrenia. [1] Greci et al. 2005, Psychopharmacology 179: 68-76 [2] Hiyoshi et al. 2014, Neurosci. Lett. 567: 30-34

Disclosures: T. Gao: None. **H. Cruces_Solis:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **H. Rosenbrock:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG. **N. Schuelert:** A. Employment/Salary (full or part-time):; Boehringer Ingelheim Pharma GmbH & Co. KG.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.06/B93

Topic: B.09. Network interactions

Support: NIH UH2/UH3 - NS95495

Title: Pre-ictal limbic coherence outside of the seizure onset zone: Considerations for the selection of normal EEG in epilepsy patients

Authors: *I. BALZEKAS, V. KREMEN, P. NEJEDLY, G. A. WORRELL;
Mayo Clin., Rochester, MN

Abstract: Epilepsy is associated with well-established changes in network activity, especially at the onset of seizures. The extent to which non-seizure onset zone (SOZ) contacts exhibit pathological changes in the hours preceding a seizure is unclear. It is possible that seizure-related, network alterations extend beyond the SOZ and begin well before seizure onset, warranting careful consideration of which brain regions and intracranial EEG (iEEG) time series can be deemed “normal” for cognitive neuroscience studies. The goal of this study was to determine if coherence between non-SOZ limbic electrode contacts change in the pre-ictal period. We identified 3 subjects undergoing iEEG monitoring for epilepsy surgery who had electrode contacts in at least two, non-SOZ limbic structures and who experienced at least one, 10-hour, seizure-free period during recording. In total, 16 electrode contacts were identified in the amygdala, hippocampus, insula, and lateral orbitofrontal cortex. The start times of 6 seizures were used to designate a one hour pre-ictal period, ending 5 minutes prior to seizure onset, and a

one hour inter-ictal period ending five hours prior to seizure onset. We calculated 3 main spectral features (delta-beta power ratio as a proxy for sleep/wake state, zero-phase lag coherence, and variance of coherence (1 minute moving window)) for each ipsilateral pair of limbic contacts using 10 second segments and frequency bands of 1-3 Hz, 3-7 Hz, 7-13 Hz, and 13-30 Hz. Features during the pre-ictal and inter-ictal periods were averaged for each subject. Wilcoxon rank-sum test was used to identify subject-specific and region-specific differences between groups. When pooled across all subjects, the pre-ictal period showed a significant decrease in beta coherence ($p < 0.01$, $n = 37$ per group). Amygdala-hippocampal alpha coherence and variance of beta coherence were significantly decreased in the pre-ictal period ($p < 0.01$, $n = 6$ per group) as was insula-hippocampal beta coherence ($p = 0.01$, $n = 8$ per group). These differences were not associated with a difference in delta coherence or delta-beta ratio between the pre-ictal and inter-ictal samples, although this study was underpowered to evaluate an interaction between coherence and brain state. In summary, these findings suggest that limbic coherence between non-SOZ contacts is altered in the pre-ictal period. Careful characterization of or omission of pre-ictal (1 hour +) iEEG may be warranted in analyses using non-SOZ contacts to investigate limbic network physiology.

Disclosures: I. Balzekas: None. **V. Kremen:** None. **P. Nejedly:** None. **G.A. Worrell:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Dr. Worrell and Mayo Clinic have a financial interest related to technologies licensed to Cadence Neuroscience Inc. and NeuroOne Inc..

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.07/B94

Topic: B.09. Network interactions

Title: Differential effects of D-amphetamine on behavior and neurophysiology during dexmedetomidine vs. ketamine anesthesia in rats

Authors: *R. KATO[1], O. MALLARI[4], E. R. ZHANG[1], E. D. MELONAKOS[1], M. SIEGMANN[5], C. J. VAN DORT[2], O. AKEJU[2], K. SOLT[3];
[1]Anesthesia, Critical Care, and Pain Med., Massachusetts Gen. Hosp., Charlestown, MA; [3]Anesthesia, Critical Care, and Pain Med., [2]Massachusetts Gen. Hosp., Boston, MA; [4]Univ. of Massachusetts Med. Sch., Worcester, MA; [5]MIT, Cambridge, MA

Abstract: D-amphetamine (d-AMPH), which causes the direct release of dopamine and norepinephrine from synaptic terminals, produces emergence from propofol and isoflurane anesthesia in rats. Dexmedetomidine (DEX) is an α_{2A}-adrenoreceptor agonist, whereas ketamine is an anesthetic that acts primarily by inhibiting N-methyl-D-aspartate (NMDA) type glutamate

receptors. These drugs produce loss of consciousness (LOC) by different mechanisms from GABAergic agents such as propofol and volatile anesthetics. In this study, we tested the efficacy of d-AMPH for accelerating recovery from DEX- and ketamine-induced LOC and recorded local field potentials (LFPs) to reveal how d-AMPH modulates neural activities in rat prefrontal cortex (PFC). LOC was defined by loss of righting, and the time to recovery of consciousness (ROC) was defined as the time from onset of saline/d-AMPH to return of righting.
After DEX (50 μg/kg IV) infusion, d-AMPH (3 mg/kg IV) administration significantly decreased the mean times to ROC from 87.2 min to 1.7 min ($p < 0.001$). When the D_1 dopamine receptor antagonist SCH-23390 (0.2 mg/kg IV) was administered prior to d-AMPH (1 mg/kg IV), the mean time to ROC increased significantly from 5.1 min to 80.3 min ($p < 0.001$). However, after ketamine infusion (50 mg/kg IV), d-AMPH (3 mg/kg IV) significantly increased the mean time to ROC from 6.3 min to 11.6 min ($p = 0.017$). When SCH-23390 (0.2 mg/kg IV) was administered prior to d-AMPH (1 mg/kg IV), the mean time to ROC increased significantly from 6.3 min to 24.6 min ($p < 0.001$). After ketamine (50 mg/kg IV) infusion, the mean time to ROC in rats that received SCH-23390 (0.2 mg/kg IV) alone was 28.7 min.
Spectral analysis of PFC LFP recordings revealed that, compared to the awake state, DEX (50 μg/kg IV) produced a sustained increase in δ (0.1-4 Hz) power that coincided with LOC. However, the administration of d-AMPH (1 mg/kg IV) after DEX promptly decreased δ power and restored an awake LFP pattern that coincided with ROC. The administration of SCH-23390 (0.2 mg/kg IV) prior to d-AMPH blocked this effect. In contrast, ketamine increased δ and γ (40-50 Hz) power, and d-AMPH administration did not affect the ketamine-induced changes in LFP power.
In conclusion, d-AMPH rapidly restores consciousness and an awake LFP pattern after DEX infusion. This effect is blocked by the D_1 antagonist SCH-23390, suggesting that the arousal effect is mediated by dopamine. However, d-AMPH does not induce behavioral or neurophysiological reversal of ketamine-induced unconsciousness. These results demonstrate that the D_1 dopamine receptor-mediated arousal effect of d-AMPH is anesthetic-dependent.

Disclosures: **R. Kato:** None. **O. Mallari:** None. **E.R. Zhang:** None. **E.D. Melonakos:** None. **M. Siegmann:** None. **C.J. Van Dort:** None. **O. Akeju:** None. **K. Solt:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.08/B95

Topic: B.09. Network interactions

Support: NCN grant 2016/23/B/NZ4/03657

Title: Nasal respiration drives 80-130 Hz oscillations in the olfactory bulb of ketamine-xylazine anesthetised rats: Implications for the NMDA receptor hypofunction model of schizophrenia

Authors: *W. SREDNIAWA[1], J. WROBEL[2], M. WHITTINGTON[3], D. K. WOJCIK[1], M. J. HUNT[4];
[1]Nencki Inst. of Exptl. Biol., Warsaw, Poland; [2]Nencki Inst. of Exptl. Biol. PAS, Warsaw, Poland; [3]HYMS, Univ. of York, York, United Kingdom; [4]Nencki Inst., Warsaw, Poland

Abstract: NMDA receptor hypofunction is used widely to model psychosis in humans and experimental animals. The neural networks which underlie the psychotomimetic actions of NMDA receptor antagonists, such as ketamine, remain poorly understood. Over the past decade we, and other groups, have shown that NMDA receptor antagonists are associated with abnormal high-frequency oscillations (HFO; 130-180 Hz) in local field potentials (LFP) recorded of awake rodents. Although HFO have been reported in multiple brain regions, the olfactory bulb (OB) appears to be particularly important for the generation of this activity. Here, we report that under ketamine (100 mg/kg) and xylazine (10 mg/kg) anesthesia (KX) a slower HFO rhythm (80-130 Hz) can be recorded from the rat OB which is comparable to that recorded in awake rats. Similar to the awake state, KX-HFO occurred as bursts that were coupled on a cycle-by-cycle basis to slower frequencies, were attenuated by unilateral naris blockade, and reversed phase close to the mitral layer. Simultaneous thermocouple (used to measure nasal respiration) and LFP recordings revealed that KX-HFO and slower oscillations, mainly delta (<2 Hz), were coupled to specific phases of nasal respiration. Further, using 32 channel silicon probes, we spatially profiled KX-HFO and delta in the OB and found HFO current sources/sinks close to the mitral layer and a large delta current source/sink more ventrally (in the extraplexiform/glomerular layers) that preceded KX-HFO occurrence. We suggest that KX-HFO emerge, due to enhanced current flow across the extraplexiform/glomerular layers, as a result of the strong delta sinks produced by nasal respiration. We conclude that KX anesthesia appears suitable for investigating aberrant HFO relevant to the awake state, which is also likely to be driven by natural breathing.

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Poster

465. Cortical Oscillations I

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Program #/Poster #: 465.09/B96

Topic: B.09. Network interactions

Support: Grant FDN-143210
Grant FDN-143209

Title: Dynamics of *in vivo* cortical network activity and local field potentials in a Huntington's disease mouse model

Authors: *M. D. SEPERS[1], J. P. MACKAY[2], E. KOCH[2], D. XIAO[1], T. H. MURPHY[1], L. A. RAYMOND[3];
[2]Psychiatry, [3]Dept Psychiatry and Ctr. for Brain Hlth., [1]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disease characterized by profound degeneration of the striatum and cortex, with patients showing progressively disordered movement and cognition. Before the onset of motor symptoms and cell death, mutant huntingtin (mHtt) expression causes abnormalities in synaptic and neuronal activity. Although the striatum is well studied in HD models, fewer studies have examined cortical neuron function in HD and in particular *in vivo* cortical network connectivity. Preliminary *in vivo* data from our labs with mesoscopic imaging using voltage-sensitive dyes (VSDs) showed a more extensive spread of evoked sensory signals across the cortical surface in YAC128 HD mice. To further examine mHtt-induced changes in the cortex, here we used tetrodes chronically implanted across various cortical areas in 6 month-old YAC128 vs. wild-type mice to measure local field potential (LFP) oscillations, and in some cases single neuron activity. Consistent with the VSD imaging experiments, our preliminary data suggest that YAC128 mice show an augmented response to evoked sensory input by limb stimulation. In multiple cortical areas instantaneous LFP power remained elevated in YAC128 longer than wild-type, particularly in beta frequencies. We also repeatedly tested awake-behaving mice to correlate spectral densities and coherence across cortical areas and used video analysis to differentiate between behavioural states: at rest, whisking, grooming and running on a wheel. The work presented here extends our knowledge of the impact of mHtt beyond *ex vivo* studies of individual neurons to the function of the intact cortical network in HD.

Disclosures: M.D. Sepers: None. **J.P. Mackay:** None. **E. Koch:** None. **D. Xiao:** None. **T.H. Murphy:** None. **L.A. Raymond:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.10/B97

Topic: B.09. Network interactions

Support: NIH Grant 5K08 NS060223
NIH Grant R01NS094748
Doris Duke Charitable Foundation Clinical Scientist Development Award #2011039

Paralyzed Veterans of America #2728

Title: High-gamma amplitude is coupled to low-gamma phase in sensorimotor cortical activity

Authors: *M. W. SLUTZKY[1], R. D. FLINT, III[2];
[2]Neurol., [1]Northwestern Univ., Chicago, IL

Abstract: Phase-amplitude coupling (PAC) in brain oscillations consists of the modulation of high-frequency amplitude according to low-frequency phase. Many studies have described PAC between low-frequency rhythms (delta, theta, or alpha bands) and high-gamma band (70-200 Hz) activity in multiple areas of the cerebral cortex, basal ganglia, and hippocampus. Here, we examined a new form of coupling between the phase of low-gamma (30-60 Hz) oscillations and high-gamma amplitude.
We computed low-gamma - high-gamma PAC in two ways: the height ratio of the phase-amplitude histogram and the mean vector length (MVL). We computed these measures on data from two monkeys and 2 human subjects. We recorded intracortical LFPs from primary motor cortex in 2 monkeys (and primary somatosensory cortex in 1 monkey) during center-out reaching tasks. We recorded subdural electrocorticography (ECoG) from the motor and premotor cortices in two humans performing grasping movements while undergoing monitoring for epilepsy. We computed the phase and amplitude of the signals using the Hilbert transform on bandpass-filtered data.
Overall, we found gamma-gamma coupling in many sites of both monkey LFPs and human ECoG. In monkey LFPs, we found that this coupling was higher in the resting position than during the first 500 ms of reaching movement (mean height ratio of 0.072 vs. 0.027, respectively, over all 96 electrodes in 2 monkeys, p=0.03, paired t-test). MVL measures also revealed substantial gamma-gamma coupling in both monkeys that decreased during movement over all electrodes.
These results point to a novel form of phase-amplitude coupling in the sensorimotor cortices. This coupling appears to be larger during idle state and smaller during movement.

Disclosures: **M.W. Slutzky:** F. Consulting Fees (e.g., advisory boards); Strategic Advisory Board for Battelle. **R.D. Flint:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.11/B98

Topic: B.09. Network interactions

Title: Functional connectivity of the cortico-thalamo-cortical circuit after interrupting spike and wave discharges with closed-loop stimulation in rats

Authors: *F. SANTOS-VALENCIA, E. URBINA-TREJO, S. ALMAZÁN-ALVARADO, A. RUBIO-LUVIANO, D. MARTÍNEZ-VARGAS;
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Abstract: High frequency electrical stimulation to deep brain nuclei has shown to be an effective way to control seizures in some forms of human epilepsy and animal models; however the way it modulates the epileptic circuits to achieve this effect is not clear. We sought to investigate this process by stimulating the cortico-thalamo-cortical circuit in an animal model of spike and wave discharges (SWD). To do this, we implanted 2 stimulation electrodes and 1 recording electrode in the right basoventral thalamus and four electrodes in bilateral motor and somatosensory cortices of Wistar rats. After 7 days post-surgery Pentylenetetrazol was injected at a single dose of 30 mg/kg of weight to induce SWDs, local field potentials (LFP) were recorded for an hour and the thalamus of half of the animals was stimulated (train duration 1s, 130Hz, biphasic squared wave 0.1ms pulses) immediately after the detection of a SWD. To deliver closed-loop stimulation band passed filtered (5-10Hz) recordings of the somatosensory cortex were input to a MATLAB program that implements the Line Length algorithm for the real time detection of SWDs (moving window 2s, time steps 0.01s). The total number of SWDs was the same in both groups and the mean percentage of interrupted SWDs in stimulated animals was 77.4%. To reveal changes in the functional connectivity of the circuit we employ wavelet coherence analysis using Morlet as the mother wavelet with 12 voices per octave. A 1s epoch following the stimulation train of interrupted SWDs was chosen for analysis; coherence was computed between the LFPs of the thalamus and the 4 cortices. We found less synchronization in the total analysis band (1-50 Hz) between the thalamus and both somatosensory cortices and in the delta (1-4Hz) and theta (4-7Hz) bands between the thalamus and both motor cortices when SWDs were interrupted. Thus, closed-loop high frequency electrical stimulation modulates the epileptic cortico-thalamo-cortical circuit by halting its intrinsic recurrent connectivity that allows the maintenance of SWDs.

Disclosures: F. Santos-Valencia: None. **E. Urbina-Trejo:** None. **S. Almazán-Alvarado:** None. **A. Rubio-Luviano:** None. **D. Martínez-Vargas:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.12/B99

Topic: B.09. Network interactions

Support: Louis Argenta Physician-Scientist Scholarship, WFSOM

Title: State-dependent variability in hierarchical phase-amplitude coupling of neural oscillations

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Abstract: Objective: A number of prior studies suggest that cross-frequency coupling between neural oscillations is functional and ubiquitous across a range of spatiotemporal scales. In this study, we studied phase-amplitude coupling (PAC) in baseline mouse local field potential (LFP) recordings over frequencies ranging from infraslow activity (below 0.2 Hz) to ripple frequencies (200 Hz). We additionally determined how PAC varied with sleep-wake state.
Methods: We computed PAC over logarithmically-distributed frequency bands ranging from 0.06 to 400 Hz in prefrontal cortex (PFC) and the CA1 region of the hippocampus in both ripple-locked and spontaneous, ongoing data. Ripple data was derived from 42, 30-minute baseline recordings across 18 animals. The spontaneous data included three 8-hour recordings from one animal. In our spontaneous data, we further determined whether sleep-wake state, as measured by the ratio of theta power to large irregular activity (LIA) power, affected the expression of PAC.
Results: In our ripple-locked data, we observed significantly nonzero ($p<0.0001$) coupling between delta and spindle frequencies, delta, and ripple, infraslow and subdelta, and infraslow and delta in all regions. In our spontaneous recordings, we found significantly nonzero ($p<0.0001$) coupling between infraslow and subdelta, and infraslow and delta activity. The magnitude of the coupling did not vary significantly by theta/LIA ratio (i.e., sleep-wake state). However, we did find spatially variable shifts in the phase of infraslow activity where subdelta and delta activity amplitude peaked.
Conclusions: We observed a hierarchical organization of PAC between infraslow, delta, spindle, and ripple activity. We speculate that the phase shifts observed in PAC with sleep-wake state in spontaneous data do not reflect shifts in the timing properties of oscillatory coupling, but rather dynamic, state-dependent spatial variability of engagement and disengagement of these oscillations.

Disclosures: R.B. Joshi: None. **D.C. Klorig:** None. **H.P. Zaveri:** None. **D.W. Godwin:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.13/B100

Topic: B.09. Network interactions

Title: Local kainate receptor expression provokes synchronous network activity in hippocampal slices

Authors: *T. KAARELA[1], W.-C. CHANG[1], T.-K. KUKKO-LUKJANOV[1], S. E. LAURI[2], T. P. TAIRA[1];
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Abstract: Kainate type glutamatergic receptors (KARs) modulate synaptic transmission and neuronal excitability depending on their subunit composition and localization. Developmental expression of KARs in the immature hippocampus is suggested to promote activity-dependent synchronization of neuronal networks, yet the exact mechanisms are still unclear. Here we asked how local manipulation of KAR subunit GluK1 modulates synchronous network activity in postnatal hippocampi *in vitro*. Multichannel recordings were used to study the spatio-temporal profile of network activity in organotypic hippocampal slice cultures. Slices were extracted from P7 male rats and cultured on multielectrode array probes with 64 planar microelectrodes (MED64). Gene expression in the CA3 pyramidal neurons was modified with injection of lentiviruses, carrying either a control (EGFP, n=12) or GluK1c over-expressing (OE, n=7) construct. Cultured hippocampi spontaneously presented alternating synchronous activities resembling ictal and interictal epileptiform discharges (IEDs) after 6 days in culture. When compared to control slices GluK1 OE did not alter the ictal activity period duration or spiking frequency. Interictal periods, however were significantly shorter ($p<0.05$, Student´s t-test), resulting in more frequent ictal discharges. In control slices, IEDs preceded the ictal discharges with increasing frequency. Interestingly, networks with GluK1 OE presented significantly fewer IEDs ($p<0.01$, Student´s t-test) which were mainly detected right before the ictal activity without the steady increase in frequency. Early IEDs originated at the CA3 and the depolarization propagated locally in the CA3 region. Prior to the onset of ictal activity, IEDs were associated with synchronous depolarizations between the CA3 and the CA1. In GluK1 OE the recruitment of the CA1 was faster, provoking the ictal initiation. Our data suggests that facilitated spatial propagation of IEDs promote synchronization of network activity in KAR expressing slices, supporting the notion that these receptors might play essential role in the functional integration of neurons in hippocampal circuitries.

Disclosures: T. Kaarela: None. **W. Chang:** None. **T. Kukko-Lukjanov:** None. **S.E. Lauri:** None. **T.P. Taira:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.14/B101

Topic: B.09. Network interactions

Support: HD87101

Title: Increased local field potential beta power in cerebral cortex of a model of Dup15q

Authors: *M. VALLEJO[1], D. TRAN[1], V. SARAVANAPANDIAN[2], J. FROHLICH[1], M. C. JUDSON[4], B. D. PHILPOT[5], S. S. JESTE[3], P. GOLSHANI[1];
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Abstract: Duplications of 15q11.2-q13.1 (Dup15q syndrome) are a frequent cause of autism spectrum disorder, intellectual disability, and epilepsy (Finucane et al. 2016). Recent studies using EEG spectral power show that children with Dup15q syndrome have dramatically increased beta band power (beta1=12-20Hz, beta2=21-30Hz) compared to typically developing children and children with non-syndromic intellectual disabilities and autism (Frohlich et al. 2016). Yet, it is poorly understood which of the many duplicated genes in the region lead to the EEG phenotype. Candidate genes include Ube3a, which is paternally imprinted and the non-imprinted α5/γ3/β3 $GABA_A$ receptor subunit gene cluster, which has been implicated in the generation of pharmacologically-induced beta oscillations (Christian et al.2015). Understanding the EEG mechanism will be critical to link this biomarker to specific molecular pathways and, furthermore, may suggest new therapies. To dissect the contribution of different duplicated genes to the beta EEG phenotype, we have performed silicon probe multielectrode array electrophysiological recordings from the parietal cortex of three Dup15q syndrome animal models during adulthood. Mice with maternally inherited 15q duplication (*mat*DP/+) overexpress Ube3a, $GABA_A$ receptor subunits genes, as well as other genes in the region (Nakatani et al. 2009,) while mice with paternally inherited 15q duplication (*pat*DP/+) do not have overexpression of Ube3a (which is imprinted) but do have overexpression of the other genes in the region (Nakatani et al. 2009). We also compared these mice to mice that exclusively express Ube3a but no other regions (generated by the Philpot lab). Similar to EEG recordings from humans, local field potential recordings from parietal cortex of *mat*DP/+ animals showed increases in both beta1 power and beta2 power, but only during locomotion [beta1:~39% 11.81 (=0.01) beta 2: ~28% 11.81 (=0.018). Two-Way ANOVA & Multiple comparison]. On the other hand, *pat*DP/+ and Ube3a overexperssor mice showed no significant changes in beta power. These results suggest that a combination of increased copy number of Ube3a and non-imprinted genes in the region (including $GABA_A$ receptor subunits) may be responsible for the abnormal beta oscillations observed in humans. Current studies are probing whether beta oscillations recruit specific populations of cortical neurons to fire in synchronization with the abnormal oscillation in Dup15q syndrome mice.

Disclosures: M. Vallejo: None. **D. Tran:** None. **V. Saravanapandian:** None. **J. Frohlich:** None. **M.C. Judson:** None. **B.D. Philpot:** None. **S.S. Jeste:** None. **P. Golshani:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.15/B102

Topic: B.09. Network interactions

Title: Computational models and phantom validation of transcranial electrical stimulation techniques for deep brain targets

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Abstract: Hippocampal theta is the largest amplitude rhythmic local field potential (LFP) in the mammalian brain. It is often associated with learning and memory due to its involvement in the timing of place cell firing. In the literature, anti-epileptic effects have been seen during theta with a dramatic reduction of epileptic discharges. Transcranial electrical stimulation (tES) techniques may provide for an advantageous method to elicit or modulate theta at low-cost and low-risk, allowing it to be easily translatable. In our lab, we tested tES methods that optimize the injected currents to target the CA1 of the hippocampus in a rat model. With 3-D reconstructions generated from MRI data that are inserted into powerful physics solvers, various electrode placements are iterated through to maximize the ratio of electric field intensity in the CA1 relative to the rest of the brain. We then validate these results by using phantom models of cleaned rat skulls filled with agar that have NaCl concentrations appropriate for the equivalent brain electrical conductivity. We have found our physics simulation results to be comparable to our phantom model results. One of the tES methods we tested is intersectional pulsing (ISP) stimulation, which is proposed to focus electric fields on deep targets by a rotation of the bipolar current injection. However, we have found ISP electric fields to be equal to the equivalent electrode placements without any rotation. The optimal tES method we have validated is temporal interference (TI) stimulation that uses two pairs of electrodes, one injecting a current of slightly higher frequency than the other causing an amplitude maximum at the difference frequency near the midline of the two pairs, thus properly targeting deeper structures. These results will guide us and other researchers to maximize the efficacy of their tES techniques when attempting to modulate neuronal oscillations of deep structures.

Disclosures: **B. Tessler:** None. **S.E. Fox:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.16/C1

Topic: B.09. Network interactions

Title: Attentional modulation of V1 (inhibitory) circuits can mediate selective V1-V4 communication through coherence

Authors: *C. KATSANEVAKI[1,2], A. M. BASTOS[1,3,4], H. CAGNAN[5,6], C. A. BOSMAN[7,8], K. J. FRISTON[9], P. FRIES[1,7];
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Abstract: The Communication-through-Coherence (CTC) hypothesis proposes that flexible effective communication among neurons depends on their coherence (Fries, Neuron 2015). Indeed, when two visual stimuli induce two local gamma rhythms in macaque V1, only the gamma induced by the attended stimulus entrains gamma in V4 and establishes coherence (Bosman et al, Neuron 2012). Additionally, attended V1 gamma shows higher peak frequency, potentially causing the selective V1-V4 coherence. Here, we investigate whether and which local modulations within V1 can result in the observed attentional effects. We used Dynamic Causal Modeling (DCM) for Cross-Spectral Densities (Friston et al, NeuroImage 2012) to fit a canonical microcircuit (Bastos et al, Neuron 2012) to macaque electrocorticographic data. DCM allows investigating the causes of the attentional effects at the microcircuit level, which is challenging to access experimentally. The data consists of triplets of two V1 sites with non-overlapping receptive fields, sending converging inputs to a V4 site. To fit the complex, non-linear models to the dataset and overcome local minima, we used Variational Laplace, introducing multiple re-initializations with stochastic updates of parameters. This novel scheme allowed us to 1) identify models with higher evidence than achieved with the conventional method, 2) show that the nature of the attentional effects in the winning model is robust across neighboring local minima and 3) show that there is an optimal level of noise that both overcomes local minima and avoids poor fitting. We find that modulation of V1 connectivity is sufficient to model the observed

attentional effects. We used Parametric Empirical Bayes to identify attentional modulations conserved over the selected triplets. The winning model suggests that attention primarily regulates inhibitory pathways within V1: Attention 1) increases the self-inhibition of superficial pyramidal cells (likely related to PV-interneuron activity), 2) increases the feed-forward excitation from layer-4 excitatory neurons to superficial pyramidal cells, 3) decreases the self-inhibition of layer-4 excitatory neurons and 4) decreases the feedback inhibition of superficial pyramidal cells onto layer-4 excitatory neurons. The latter two inhibitory effects can be mediated by local inhibitory interneurons in layer 4. The probability of those attentional modulations across the top 5% of models is 0.88, 0.94, 0.87 and 0.93, suggesting their crucial role. Thus, attentional modulations within the V1 circuitry, primarily of inhibitory connections, can explain increased V1 gamma frequency and enhanced V1-V4 gamma coherence.

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Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.17/C2

Topic: B.09. Network interactions

Title: Amplitude-modulated high-frequency electric field stimulation of gamma oscillations *in vitro*

Authors: *Z. ESMAEILPOUR[1], G. KRONBERG[2], L. C. PARRA[3], M. BIKSON[4];
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Abstract: It has been suggested that amplitude-modulated high-frequency (>1 kHz) electrical stimulation has special biophysical or neurophysiological features that can be leveraged in neuromodulation, including applications of transcranial electrical stimulation (tES) and inferential stimulation (IF). Explaining the cellular mechanism of amplitude-modulated high-frequency stimulation is thus of interest in neuromodulation. Yet, the well-established low-pass filtering by neuronal membranes suggests minimal neuronal polarization in response to continuous charge-balanced high-frequency stimulation, regardless of any underlying modulation. The hippocampal brain slice model is among the most characterized systems in neuroscience and exhaustively characterized in screening the effects of electrical stimulation. Effect of amplitude-modulated high-frequency electric fields on ongoing network activity was evaluated in carbachol-induced gamma oscillation in CA3a region of rat hippocampal slices. Extracellular local field potentials were recorded and analyzed before, during and after 2 s of

stimulation. We tested kHz frequency carriers with low-frequency modulation such that the resulting waveform alternates between low and high amplitude phases every tens of ms, with tens of kHz oscillations per modulated phase. The hippocampal brain slice model of gamma oscillation provided a rapid experimental system to test the degree of modulation produced by amplitude-modulated high-frequency stimulation as well as control waveforms of fixed amplitude kHz stimulation and simple low-frequency sinusoidal stimulation. We further developed a computational model of excitatory/inhibitory neuronal network with conductance-based synaptic interactions. kHz oscillations in the high phase driving singe neuron activity, with loss of efficacy determined by linear membrane low-pass characteristics and accommodation. The inter-phase period drives oscillations determined by non-linear network characteristics. These simple rules explain a broad range of findings. Inferential waveforms require significantly more intensity than simple low-frequency sinusoids (as used in transcranial Alternating Current Stimulation, tACS), may be ineffective at intensities relevant for clinical transcranial stimulation (compared to tACS), and would be increasingly ineffective with higher kHz carriers (e.g. 2 kHz). The lack of response to continuous fixed amplitude kHz stimulation does not reflect a special sensitivity to the modulation, but rather accommodation to steady stimulation.

Disclosures: Z. Esmaeilpour: None. **G. Kronberg:** None. **L.C. Parra:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); City college of new york. **M. Bikson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); City college of new york.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.18/C3

Topic: B.09. Network interactions

Support: NSF Grant CMMI-1826065

Title: Communication through coherence: Analysis of the optimal phase shift and the importance of waveform shape

Authors: *E. NOZARI[1], J. CORTES[2];
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Abstract: According to the communication through coherence hypothesis, the causal effect of one oscillatory circuit on another is maximized if the two are phase-locked and their phase shift is "optimal", i.e., such that the sender signal arrives at the receiver at the peak of its excitability. It is often postulated that this optimal phase shift is the same as the stable phase shift, i.e., the

phase shift that the two oscillators naturally converge to in the steady state. However, the computation of the stable phase shift often requires (accurate) computational models of the underlying dynamics. Furthermore, even though it has been long known that heterogeneity can alter the stable phase shift of coupled oscillators, analyses have been primarily focused on synchronous and anti-phase relationships (phase shifts of 0 and 180 degrees) modulo the effects of delays. In this work, we seek to characterize the stable phase shift of pairs of heterogeneous and non-sinusoidal coupled oscillators in terms of their waveform shapes.
We first define a waveform synchronization centroid (WSC), computed independently for each oscillator, which coincides with the peak of sinusoidal waveforms but may be significantly off-peak for general ones. We then show that the stable phase shift of same-frequency weakly-coupled oscillators is equal to the difference of the phases of their WSC, i.e., the oscillators slide with respect to each other until their WSCs are aligned. The computation of WSC, however, still requires knowledge of the computational model of each oscillator. We thus analyze the optimal phase shift that maximizes the cross-correlation function (closely related to coherence index) and the linear-threshold causal effect (as a deterministic measure of information transfer), which depend only on the waveforms. We analytically prove that, for sinusoidal oscillators, correlation and causal effect are maximized exactly when the two oscillators are phase-locked with zero phase shift. However, neither this direct relationship between cross-correlation and causal effect nor the optimality of zero phase shift are generally true for oscillators with non-sinusoidal waveforms. In the latter case, we observe that the difference in WSC is better explained by the phase shift maximizing the causal effect rather than the one maximizing cross-correlation.

Disclosures: **E. Nozari:** None. **J. Cortes:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.19/C4

Topic: B.09. Network interactions

Support: R01-MH087755

Title: Intrinsic gamma mechanisms differ in model lateral and basal amygdala networks

Authors: ***F. FENG**[1], D. HEADLEY[2], D. PARE[2], S. NAIR[1];
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Abstract: The basolateral amygdala (BLA) is recognized as being important for mediating learned emotional behaviors. Consistent with this view, *in vivo* LFP recordings from rodent BLA during states of emotional arousal reveal gamma oscillations (30-100 Hz) that are thought to

facilitate communication with downstream targets and coordinate local activity. However, BLA is heterogeneous with distinct lateral (LA), basal (BL) and accessory-basal (AB) subdivisions, and the role of these distinct nuclei in generating and supporting gamma oscillations is presently unclear.
We have recently found that gamma in LFP recordings differ significantly between LA and BL regions. For instance, spontaneous gamma oscillations were prominent in BL but not in LA. However, gamma power in LA was found to be significantly higher during task-related events. Differences in microcircuitry and extrinsic inputs between the regions might explain these observations. For instance, although it is known that gamma oscillations emerge from reciprocal interactions between pyramidal cells (PNs) and parvalbumin-expressing fast spiking inhibitory interneurons (FSIs), it is also recognized that subtle changes in the connectivity and synaptic strengths of this microcircuit affects the properties of gamma. The link between microcircuitry differences and gamma properties is difficult to explore experimentally. Hence, we used large-scale biophysical computational models of LA and BL that incorporate known connectivity as well as cellular and synaptic neurophysiology to explore this question.
In vivo extracellular recordings from LA and BL revealed differences in cell proportions of PNs and FSIs, connectivity between the cell types, and firing rates during different states. Furthermore, it is also known that LA and BL differ in their afferent connections. After incorporating data related to connectivity and cell proportions, model synaptic strengths were tuned to replicate the firing rates and gamma characteristics of the specific region, LA or BL. The new network parameters also reproduced what was found *in vivo* and in earlier models. We found that the sparser connectivity in LA, compared to BL, necessitates significantly higher inhibitory synaptic strengths (FSI-PN) in the LA model to match *in vivo* firing rates. These models provide a path forward to understanding the mechanisms underlying gamma oscillations in the BLA and exploring how they affect local computations.

Disclosures: **F. Feng:** None. **S. Nair:** None. **D. Headley:** None. **D. Pare:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.20/C5

Topic: B.09. Network interactions

Support: NIH Intramural Research Program

Title: Alpha oscillations rhythmically modulate large-scale functional connectivity in the human cortex

Authors: *J. I. CHAPETON, R. HAQUE, J. H. WITTIG, JR, S. K. INATI, K. A. ZAGHLOUL;
NIH, Bethesda, MD

Abstract: Neural oscillations are ubiquitous in the human cortex and appear at multiple temporal and spatial scales, however, the functional significance of these rhythms continues to be a topic of intense debate. Recent evidence has suggested that coherent neuronal oscillations may serve as a gating mechanism for flexibly modulating communication between brain regions. Given that a brain region may send and receive connections from multiple other regions, synchronized oscillations could allow for communication between brain regions to be modulated without requiring substantial changes to the underlying structural connectivity. This is the basic principle behind models of oscillation-mediated communication such as communication through coherence and communication through resonance.

Alpha oscillations are the canonical example of rhythmic neural activity in the human brain and appear to be particularly well suited for mediating large-scale synchronization. This is because they are robust in terms of power and frequency and can be readily observed throughout the human cortex. Here, we test the hypothesis that large-scale communication in the human brain is modulated by coherent oscillations in the alpha band by investigating human intracranial EEG (10 participants) and micro-electrode recordings (2 participants) captured from awake, freely behaving participants as they were being monitored for seizure activity. Based on theoretical considerations related to the implementation of communication schemes that depend on oscillatory entrainment or resonance, we identified a set of constraints which must be satisfied if alpha oscillations are to modulate large-scale communication. By analyzing functional connectivity in both the time and frequency domains, we demonstrate that alpha oscillations satisfy these constraints and are well suited for modulating communication over large spatial scales in the human brain.

Specifically, we find robust alpha oscillations that are coherent between brain regions with center frequencies that are specific to each individual participant. Regions demonstrating coherent narrowband oscillations also exhibit time-locked broadband correlations with a consistent time delay, as required for an efficient communication channel. The phase lags of the coherent alpha oscillations match the time lags of the correlated components, and importantly, both broadband correlations and neuronal spiking activity are modulated by the phase of the oscillations. These results are specific to the alpha band and provide evidence that large scale communication in the human brain may be rhythmically modulated by alpha oscillations.

Disclosures: J.I. Chapeton: None. **R. Haque:** None. **J.H. Wittig:** None. **S.K. Inati:** None. **K.A. Zaghloul:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.21/C6

Topic: B.09. Network interactions

Support: NSF-CMMI1435358
NIH DC015137

Title: Enhancing the synchronization of coupled gamma rhythms through intrinsic network heterogeneity

Authors: *X. XU, H. RIECKE;
Applied Mathematics, Northwestern Univ., Evanston, IL

Abstract: The synchronization of gamma rhythms in different brain areas has been implicated in some cognitive functions. Here, we focus on the effect of neural heterogeneity on the synchronization of such rhythms, which are associated with PING (pyramidal-interneuronal network gamma) rhythms or ING (interneuronal network gamma) rhythms. The synchronization properties of rhythms depends on their phase response to external input. Therefore, we determined the macroscopic phase-resetting curve for finite-amplitude perturbations (fmPRC), using numerical simulation of all-to-all coupled networks of integrate-and-fire neurons exhibiting gamma (either PING or ING) rhythms. Importantly, the delayed coupling between excitatory (E) and inhibitory (I) cells or between I and I cells was strong. We show that the intrinsic neural heterogeneity can strongly modify the fmPRC. While the infinitesimal mPRC is strictly positive, for sufficiently large perturbations the fmPRC can become biphasic. Thus, for PING rhythms, an external excitation to the E cells can not only advance but also delay the network depending on the time when it is applied, even though the same excitation would only lead to an advance when applied to uncoupled neurons. The delay arises when the excitation causes additional spikes of inhibitory neurons, whose delaying impact outweighs the external excitation. These results explain how the intrinsic heterogeneity allows the PING rhythm to become synchronized (either accelerated or decelerated) to a periodic external excitatory force and, by extension, to another PING rhythm. The persistent relationship between two coupled phase-locking rhythms then can be understood as the stable point on the fmPRC. Based on the dependence of the fmPRC on the heterogeneity, we numerically show that for larger intrinsic heterogeneity, coupled PING rhythms can be synchronized for a wider range in the mismatch of their frequencies. A similar mechanism is found for the synchronization of ING rhythms. Our results identify a potential function of neural heterogeneity in the synchronization of coupled gamma rhythms, which may play a role in neural information transfer via communication through coherence.

Disclosures: **X. Xu:** None. **H. Riecke:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: B.09. Network interactions

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Medical Research Council MC_UU_12024/3

Title: Dynamics in oscillatory waveform shape revealed by empirical mode decomposition

Authors: *A. J. QUINN[1], V. LOPES-DOS-SANTOS[1], W.-K. LIANG[2], C.-H. JUAN[2], J.-R. YEH[2], N. HUANG[3], D. DUPRET[1], A.-C. NOBRE[1], M. WOOLRICH[1];
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Abstract: The waveform shape of the hippocampal theta oscillation shows large variability between cycles, though the physiological and behavioural relevance of this is not well understood or accounted for in current models of hippocampal theta function. Changes in theta waveform shape that prolong the duration of a particular theta phase may facilitate the gamma oscillations and cell spiking nested within that theta-phase. As such, waveform shape variability may be a relevant feature for computations within the Hippocampus. Here, we characterise waveform shape with the Instantaneous Frequency (IF) of an oscillation isolated by masked Empirical Mode Decomposition (EMD). IF is estimated from the differential of the phase and quantifies how quickly an oscillation is progressing through a cycle at a given point ie how quickly or slowly the cycle is progressing at that point. Crucially, this may be estimated at the full sampling rate of the observed data allowing measurement of within-cycle variation of IF. Differences in cycle duration and timing between features are normalised across cycles by interpolating each cycle's IF to a regularly sampled phase grid. This phase-aligned IF allows for direct comparisons at each point in the phase despite variations in their absolute and relative timing of each cycle. The variance of phase-aligned IF is taken as a summary of waveform shape. This method is applied to LFP data recorded from CA1 in the Hippocampus of 8 mice across 46 open field recording sessions. The waveform shape across all theta cycles is explored in a 2d space coding each cycles peak and edge asymmetry revealing a tendency towards high-frequency ascending edges and low frequency descending edges. In contrast, there is a wide variety in peak asymmetry with both fast peak cycles and fast troughs cycles occurring with

similar prevalence. A two-level multivariate GLM was used to quantify the relationship between waveform shape, movement speed and novel/familiar environment, with covariates of theta cycle amplitude and theta cycle average frequency. This shows that theta waveform shape is differentially modified by both movement speed and environment novelty. Finally, change in theta waveform shape modulates higher-frequency theta nested oscillations whiles covarying out the effects of movement speed, theta amplitude and theta frequency. Shape analysis through phase-aligned IF shows that theta waveform-shape is a measurable and relevant feature showing rapid dynamics and strong covariance with movement speed and theta-nested oscillations.

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Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.23/C8

Topic: B.09. Network interactions

Support: Whitehall Foundation (2017-12-73)
National Science Foundation (1736028)
NSERC PGS-D
KIBM IRG

Title: Hierarchy of cortical population characteristic timescales inferred from field potentials

Authors: *R. GAO[1], B. VOYTEK[2];
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Abstract: Neuronal populations across the macaque cortex exhibit intrinsic characteristic timescales in their spiking fluctuations. Specifically, sensory areas have shorter timescales of spiking autocorrelation (i.e., faster decay), while frontal areas have longer timescales [1]. Importantly, these regional differences predict working memory function, suggesting possible physiological mechanisms for how populations temporally maintain information [2]. Extending measurements of population timescales across many brain regions would considerably broaden our understanding of neurodynamics and how they support behavior. However, it is prohibitively expensive and technically challenging to record single units across the whole macaque cortex under different tasks, and impossible in the human brain due to the scarcity of single-unit recordings, even in rare clinical settings.
Here we infer neuronal population timescales from field potentials recorded via

electrocorticography (ECoG) grids across the macaque and human cortex. In frequency domain, the power spectral density (PSD) of field potentials often have a 'knee' [3] connecting two distinct power law-like regimes. The frequency at which this knee occurs corresponds mathematically to the time constant of autocorrelation decay in time domain. Applying a spectral parameterization tool we developed on 8 whole-cortex ECoG recordings from 2 monkeys [4,5], we find that ECoG timescales are tightly correlated with the reported spiking fluctuation timescales in select cortical areas from [1]. Furthermore, we extend the analysis to resting ECoG recordings from 106 human patients (1772 electrodes total) undergoing epilepsy monitoring [6]. We find that intrinsic timescale of electrode groups in each brain region increases with distance from the respective primary sensory (or motor) area, and that frontal lobe timescales, in particular, decreases with age. We validate the method with simulation of varying timescales, and discuss results pertaining to the scale-free nature of neuronal activity. In summary, this work offers a method for characterizing neuronal population timescales without single-unit measurements, which can be extended to M/EEG and field potential data in humans and other model organisms. [1] Murray et al., 2014, Nature Neuroscience[2] Wasmuht et al., 2018, Nature Communication[3] Miller et al, 2009., PLoS Computational Biology[4] Haller, Donoghue, et al., 2018, bioRxiv[5] Yanagawa et al., 2013, PLoS ONE (NeuroTycho Database, www.neurotycho.org)[6] Frauscher et al., 2018, Brain

Disclosures: R. Gao: None. **B. Voytek:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.24/C9

Topic: B.09. Network interactions

Title: Assessing how periodic oscillation properties influence estimates of aperiodic neural activity

Authors: *A. HOHIL[1], R. GAO[2], B. VOYTEK[3];
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Abstract: In this work, we investigate if nonstationarity and nonsinusoidality (i.e., the waveform shape) of oscillations can cause a change in the estimate of the aperiodic component. Since these components are not independently controllable in real data, we simulate data in the time series, and independently vary periodic and aperiodic parameters in the simulation, while observing changes in the retrieved parameters of the power spectrum in analysis. This allows us to see which periodic oscillatory parameters confound estimates of aperiodic components, enabling us

to make more reliable claims about the physiological processes that generate oscillatory and aperiodic signals in the brain.
Mesoscale electrophysiological signals recorded in the brain, such as the local field potential (LFP), reflect postsynaptic current fluctuations that are largely aperiodic. However periodic neural oscillations can wax and wane, are often bursty, nonstationary, and nonsinusoidal (Cole and Voytek, 2017). These aperiodic and periodic components can be separated in the frequency domain representation of the signal (power spectrum), a 1/f-like signal with narrowband oscillatory peaks rising above it. Notably, recent research demonstrates that these different components likely index different physiological properties. In particular, the aperiodic exponent (slope) correlates with the excitation and inhibition ratio of the local circuit (Gao et al., 2017). Behaviorally, the aperiodic component correlates with task engagement, cognitive load, and aging, in which the slope of the aperiodic component in older adults has shown to flatten with age.
However, these interpretations assume that the aperiodic and periodic components arise from separate and independent processes, which has not been explicitly examined. Under this assumption, features of the oscillation such as frequency shift, nonsinusoidality, etc. do not impact the estimate of the slope. But it is currently unknown if and how changes in oscillatory features can also bias the slope estimate of the aperiodic component in the frequency domain, thus confounding interpretations of oscillatory vs. aperiodic processes in the brain.

Disclosures: **A. Hohil:** None. **R. Gao:** None. **B. Voytek:** None.

Poster

465. Cortical Oscillations I

Location: Hall A

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Topic: B.09. Network interactions

Support: Deutsche Forschungsgemeinschaft through the Collaborative Research Center 889 “Cellular Mechanisms of Sensory Processing” to S.T. (Project C04)
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Title: Phase-amplitude coupling mediates sensory-motor integration in the macaque visual cortex

Authors: M. B. KHAMECHIAN[1], S. TREUE[2], ***M. ESGHAEI**[2], M. R. DALIRI[1];
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Abstract: Visually-guided behavior requires the integration of information across several brain areas, to generate motor responses based on visual inputs. For this, sensory information encoded in the visual areas needs to be transmitted to the motor cortex. However, the neural mechanisms underlying this integration have remained elusive.
We recorded extracellular activities from the middle temporal area (MT) of two macaques while they performed a change detection task, requiring them to report a subtle change in the direction of a coherently moving random dot pattern (RDP). Based on the monkey's response time (RT) in each trial we divided the trials into a fast and a slow subset. We next extracted the local field potentials (LFP) and calculated the phase-amplitude coupling (PAC) for the period before the direction change, and compared the PAC between fast and slow trials in different frequency pairs. Our data show that fast trials have a significantly higher PAC between the beta band's phase (10-25 Hz) and high-gamma band's amplitude (180-220 Hz) for the interval preceding the animal's response. This indicates that local neural activities in visual cortex (reflected in high-gamma oscillations) more likely occur at a specific phase of the beta band oscillations in fast trials. This suggests that an enhanced beta high gamma PAC helps transferring the sensory signals to higher level sensorimotor areas, including the motor cortex. Our data propose a novel neural mechanism through which the information transfer from sensory to motor areas could be enhanced via synchronizing neural activities in different frequencies.

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Poster

465. Cortical Oscillations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 465.26/C11

Topic: B.09. Network interactions

Support: CONACYT-SEP-CB 250930

Title: Probabilistic characterization of Fast ripple parameters in a temporal lobe epilepsy model by Bayesian inference

Authors: *M. A. NUÑEZ-OCHOA, G. CHIPRÉS-TINAJERO, N. GONZÁLEZ-DOMÍNGUEZ, L. G. MEDINA-CEJA;
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Abstract: Epilepsy represents a global public health problem, in particular, temporal lobe epilepsy (TLE) is a subtype of the pathology that is highly refractory to pharmacological treatment and therefore, generally referred to surgical intervention and it is very important to develop new paradigms of approach to the diagnosis and treatment of this disease. The high-

frequency oscillation in the range of 250 to 600 Hz, also known as Fast ripple (FR), is becoming increasingly important as a biomarker for detecting epileptogenic zones, since they are observed exclusively in epileptic foci, both in experimental models and in patients with TLE. The origin of this activity is strongly associated with synaptic modifications related to the pathological process of TLE and characterizing the properties of the FR signal between different regions of the brain could explain intrinsic characteristics of the underlying neuronal circuits; in addition, once characterized, the parameters could be used to evaluate pharmacological or surgical interventions contrasting changes in these. The aim of the present study was to construct the probability distributions of means and standard deviations of the following FR parameters: Peak to peak voltage, power frequency, power and duration between three different regions of the trisynaptic circuit. Six adult male Wistar rats (210 - 300g) were used for this study to induce the epilepsy model; the rats were injected into the right lateral ventricle (AP: -4.5 mm, ML: -5.2 mm y DV: -7 mm) with a single dose of pilocarpine hydrochloride (2.4 mg/2µl) through a needle connected to an injection pump attached to the stereotaxic framework (Stoelting Co. IL. USA); these animals were video-monitored 24 hours/day in order to detect spontaneous and recurrent seizures, once detected, rats were oxygen-isoflurane anesthetized and fixed to the stereotactic frame. Fixed-recording tungsten wire electrodes (60 µm outer diameter), consisting of pairs with a 500 µm vertical tip separation, were implanted into the Dentate Gyrus, CA3, and CA1, all microelectrodes were implanted ipsilateral to the pilocarpine injection; a total of 346 FR were recorded, then Bayesian inference was used to estimate the joint posterior probability distributions of the parameters. In a satisfactory way, we constructed the credibility regions (joint posterior probability distributions) of the studied parameters between the different regions of the trisynaptic circuit according to our inclusion criteria used in the present study.

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Poster

465. Cortical Oscillations I

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Program #/Poster #: 465.27/C12

Topic: B.09. Network interactions

Support: NIH Grant 5R01DC015260-03

Title: Exercise acutely increases the coupling between hippocampal and neocortical ripples in humans

Authors: A. RAMIREZ-CARDENAS[1], C. K. KOVACH[1], J. F. RAMIREZ-VILLEGAS[3], R. C. COLE[2], A. GROSSBACH[4], P. E. GANDER[1], H. KAWASAKI[1], J. D. GREENLEE[1], M. A. HOWARD, III[1], ***M. W. VOSS**[5];

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Abstract: Physical exercise improves hippocampal-based learning and memory in rodents and humans. Recent data highlight the importance hippocampal circuits to these performance benefits. Beyond improvements in long-term potentiation and synaptic plasticity mechanisms in rodents, the electrophysiological basis for exercise-induced effects on human hippocampal-cortical circuits is unknown.

However, there is a growing understanding of electrophysiological mechanisms supporting hippocampal-based learning and memory. Slow field potential deflections and high frequency oscillations in the hippocampus, known as 'sharp wave-ripple' (SWR) complexes, are thought to play a critical role in memory consolidation and retrieval across sleep and awake states. More recently the occurrence and functional role of ripples in the neocortex has also been recognized (Frauscher et al. 2018; Guragain et al. 2018). In both rodents and humans the coupling between hippocampal and neocortical ripples has been observed in association with learning and memory retrieval (Khodagholy et al. 2017; Vaz et al. 2019). These recent findings relate ripples to acute modulation of coupling between the hippocampus and association cortices. Further, physical exercise has been shown to increase hippocampal-cortical functional connectivity both immediately and after months of training (Voss et al., 2019). Yet, the data from exercising humans depends exclusively on hemodynamic measures of functional connectivity and cannot speak to the electrophysiological mechanisms.

Thus, we obtained electrocorticographic and depth-electrode recordings in 13 epileptic surgical candidates with coverage of both hippocampal-entorhinal and medial-prefrontal regions during awake resting state, before and after acute exercise. Heart rate, respiratory frequency and skin conductance were continuously monitored. Contacts in seizure onset zone and those where epileptic events were determined were excluded.

Results show, for the first time, that hippocampal-cortical coupling associated with ripples in humans is altered in the awake resting state acutely after exercise. Specifically, synchrony between high-frequency oscillations in the hippocampus and medial prefrontal cortex increased and was maintained when using a variety of signal-referencing and ripple detection methods. We also show that low frequency-gamma phase-amplitude coupling between pairs of hippocampal contacts is increased after acute-exercise. These findings elucidate potential electrophysiological mechanisms by which physical exercise could improve human memory.

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Poster

465. Cortical Oscillations I

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Topic: B.09. Network interactions

Support: NIH Grant R01 EY026156
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Title: Dynamics of state transitions in local laminar circuits

Authors: *N. KHARAS, S. R. DEBES, A. R. ANDREI, V. DRAGOI;
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Abstract: Spontaneous fluctuations in neuronal firing are observed at the timescale of milliseconds. Traditionally, synchronized neural activity was characterized as ON and OFF state transitions during sleep, whereas desynchronized activity was viewed as a hallmark of wakefulness. However, recent studies have indicated that ON and OFF states are present during wakefulness, but the prevalence of synchronized activity and its dependence of behavioral state remain unclear. To determine whether synchronized fluctuations in ON and OFF states occur in different behavioral states, we recorded single- and multi-unit activity along a cortical column in monkey visual cortex (areas V1 and V4) while animals performed a behavioral task or were sleeping. We subsequently employed a hidden Markov model to identify ON and OFF response states in neuronal populations, and measured the frequency of transitions between the two states within a column. The number of transitions per second between states was significantly greater in sleep than in wakefulness. The trial-by-trial frequency of the transitions was negatively correlated with the global brain state measured by arousal. We further examined the presence of synchronized state transitions in the supragranular, granular, and infragranular layers of V1 and V4 during wakefulness, and discovered that synchronized fluctuations in population activity were rare events across layers. Furthermore, we induced ON and OFF state transitions using optogenetics stimulation in one cortical layer to determine whether synchronized fluctuations spread towards adjacent layers. However, the rapid fluctuations in cortical activity caused by light did not propagate to other layers despite strong inter-layer connectivity. Our findings indicate that cortical laminar networks operate in a desynchronized mode during wakefulness and switch to synchronized activity during sleep.

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Poster

466. Memory Systems

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Title: Computational changes in the hippocampus and entorhinal cortex in TLE

Authors: *W. P. CLAWSON, P. P. QUILICHINI, C. BERNARD, D. BATTAGLIA;
Inst. de Neurosciences des Systemes, Aix-Marseille Univ., Marseille, France

Abstract: Neural computation occurs within large neuron networks in the dynamic context of varying brain states. In our previous work (Clawson et al., Science Advances 2019) we have shown that during both anesthesia and sleep specific subsets of "computing hub neurons" perform well defined information processing operations (storage and sharing) in a brain state-dependent manner. Different sets of computing hubs are recruited in different computing substates, a multitude of which exist within each global brain state. Furthermore transitions between different substates occur spontaneously, forming complex sequences whose syntax is neither regular nor random but complex, i.e. standing between order and disorder. We generalize here our novel analysis framework to the new case of Temporal Lobe Epilepsy (TLE). TLE is associated with a variety of functional deficits. However, how TLE effects the underlying algorithmic behavior of neuronal ensembles is unknown. Using acute high-density recordings in the hippocampus and entorhinal cortex in the induced TLE rat model we identify computing substates using a similar approach as our previous work. The aim is to compare the properties of hub neurons as well as the computational substates of the recorded regions to previously reported results in control animals. We find that the likelihood that a neuron assumes the role of a computational hub is decreased while the identified sequences of substates expressed are on average, less complex. We propose that the underlying biological changes which occur during status epilepticus disrupt the algorithmic patterns in such a way that may cause functional deficits. However, applying these methods to behavioral data would be needed to further test this hypothesis.

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Poster

466. Memory Systems

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ANR ERMUNDY
NeuroPole
Fonds Paul Mandel

Title: Are there discrete gamma sub bands in hippocampal networks during spatial navigation?

Authors: *V. DOUCHAMPS[1], S. FERTE[1], D. BATTAGLIA[2], R. GOUTAGNY[3];
[1]Univ. of Strasbourg, Strasbourg, France; [2]INS, Univ. Aix-Marseille, Marseille, France; [3]CNRS UMR7364, Strasbourg, France

Abstract: Theta and gamma oscillations are believed to organise hippocampal activity. The classic view suggested that two gamma sub-bands, occurring at different theta phases, are related to encoding and retrieval of spatial information. Recent evidence suggested that there is in fact a wider repertoire of theta-gamma patterns of coupling, indicating that, in the CA1 area of the hippocampus, each theta cycle has an individual profile of gamma features. We thus aimed at investigating whether the dentate gyrus shows a similar pattern of theta-gamma coupling dynamics during the learning of a spatial reference memory task. To do so, we developed a new task based on a radial maze presenting marked decision points (exit/entry of each arm). We examined the difference between the CA1 and dentate gyrus cellular layers across learning of the task by CD1 mice implanted with a linear multielectrode in the right dorsal hippocampus (n=3). We extracted, without a priori, the dominant gamma frequencies from the LFPs using an unsupervised ensemble empirical mode decomposition method. We reliably found two intrinsic mode frequencies with a peak power around 45 and 80 Hz, corresponding broadly to the gamma sub-bands classically described. The power of these intrinsic mode frequencies increased with training, although more strongly in CA1. We further performed a theta cycle-by-cycle analysis of the gamma (30-200 Hz) power in the composite gamma signal (from the intrinsic mode frequencies with a frequency within gamma range). We used an unsupervised algorithmic approach to identify typical gamma bursting patterns during theta cycles. Strikingly, we found that a continuum of gamma burst types exist, with the peak gamma frequency being strongly correlated with the running speed, in both CA1 and the dentate gyrus. However, this continuous repertoire is sampled in an "edge-of-chaos" manner, giving rise to sequences of bursts with fast switching frequencies, despite the lack of gaps between sub-bands. In conclusion, our results contrast with scenarios proposing only a discrete number of mostly mutually-exclusive gamma

types. We are now investigating how the theta-gamma oscillatory bursting dynamics (statistics of temporal sequences...) evolve across learning and as a function of the behavioral strategy employed by the animal to solve the task.

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Poster

466. Memory Systems

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Title: Temporal network analysis of hippocampal computing hubs and state sequences

Authors: *N. PEDRESCHI[1], W. CLAWSON[1], C. BERNARD[1], P. P. QUILICHINI[1], A. BARRAT[2], D. BATTAGLIA[1];
[1]Aix-Marseille University, INS, Marseille, France; [2]CPT, Univ. Aix-Marseille, Marseille, France

Abstract: Neural computation occurs within large neuron networks in the dynamic context of varying brain states. In our previous work (Clawson et al., Science Advances 2019) we have shown that during both anesthesia and sleep specific subsets of "computing hub neurons" perform well defined information processing operations (storage and sharing) in a brain state-dependent manner. Different sets of computing hubs are recruited in different computing substates, a multitude of which exist within each global brain state. Furthermore transitions between different substates occur spontaneously, forming complex sequences whose syntax is neither regular nor random but complex, i.e. standing between order and disorder. In our previous work, however, we have not analyzed in detail the temporal variability of functional connectivity networks between single units, occurring both within consistent computing substates and across substates.
Here we use a sliding window approach to estimate time-dependent networks of information sharing among tens of single units in hippocampus and enthorinal cortex during anesthesia. We adopt then a temporal network formalism, generalized from analyses first introduced in social network studies, to characterize the "style" of temporal variability of these networks.
We find first that these functional connectivity networks have at any time a characteristic core-periphery structure, in which segregated units are connected as network leafs to an integrated assembly of more tightly functionally interconnected units. However the exact units participating to the core or to the periphery substantially change across time-windows, with new units entering

and other leaving the core in a "liquid" way.
Furthermore in such a temporal network description framework, new notions of hubness can be introduced. Some cells can share information with a multitude of other units but only in a quite intermittent manner, as "activists" in a flash mob. Other cells can on the contrary share information with a smaller number of other units, but do so in a more steady manner, as "whisperers" to influential nodes. Through an unsupervised classification approach we extract different types of temporal hubness styles and assign them to each different cell, showing that: anatomical localization only poorly influence the style of temporal connectivity that a cell can have; a cell can change style of temporal connectivity across different computing substates. Altogether our study reveal the potential unleashed by upgrading from a static to a temporal network perspective current functional connectivity analyses of multichannel electrophysiological recordings.

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Poster

466. Memory Systems

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Topic: B.09. Network interactions

Support: The National Centre of Research and Development (grant no 01.02.00-00-0023/17-001).

Title: The effect of subthreshold and threshold stimulation of the vagal nerve on hippocampal formation theta rhythm in anaesthetized rats

Authors: ***J. KONOPACKI**[1], A. BRONCEL[2], R. BOCIAN[1], P. KŁOS-WOJTCZAK[2]; [1]Dept. of Neurobio., Univ. of Lodz, Lodz, Poland; [2]Med. Technol. Ctr., Natolin, Poland

Abstract: Just recently it was demonstrated that vagal nerve stimulation (VNS) is capable of inducing hippocampal formation (HPC) theta rhythm (Broncel et al., 2017). The neuronal substrate underlying this novel phenomenon is poorly known. The cholinergic and GABAergic profile of VNS-induced theta rhythm in anesthetized rats has just recently been addressed (Broncel et al., 2018, Broncel et al., 2019). In a present study we extended our earlier observation concerning VNS-induced theta oscillations. Specifically, the purpose of the present study was to compare the subthreshold and threshold stimulation of the vagal nerve on HPC theta rhythm. The advantage of using model of VNS-induced theta rhythm is that it allows analysing the effects of subthreshold stimulation and the effects of threshold stimulation. The definition of subthreshold stimulation of vagal nerve adopted in a present study concerns the

delayed effect that could be observed when low VNS intensity (0.4-2.0 mA) is applied a few times in strictly defined intervals. This kind of VNS protocol allows registration of well-developed theta rhythm which appears with a delay of even a dozen min. The definition of threshold stimulation of vagal nerve concerns the effect of VNS applied with higher intensity (6-8 mA). In this case HPC theta appears directly and only during stimulation. These results have some clinical implication. VNS is indicated in patients with pharmacotherapy resistant epilepsy. The existence of VNS-responders and VNS non-responders may reflect direct and delayed neural processes of stimulation of vagal nerve fibres.

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Poster

466. Memory Systems

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Topic: B.09. Network interactions

Support: CIHR grant MOP 137072

Title: Several distinct types of VIP-expressing GABAergic neurons reside in the stratum lacunosum moleculare of the mouse CA1 hippocampal region

Authors: *B. MARINO, L. TOPOLNIK;
Laval Univ., Quebec City, QC, Canada

Abstract: The vasoactive intestinal peptide-expressing (VIP+) GABAergic neurons in the CA1 hippocampus provide a widespread control over local circuit inhibition. The hippocampal VIP+ neuronal population is highly heterogeneous, comprising cells with distinct properties, connectivity and recruitment to network activity *in vivo*. The cellular architecture, regulation and function of hippocampal VIP+ cells remain still largely unknown. Here, we examined the cellular diversity of the type II VIP+ interneuron-specific interneurons that have soma located within the CA1 *stratum lacunosum moleculare* (LM) and have been suggested to contact several distinct types of interneurons in *stratum radiatum* (RAD). Using whole-cell patch-clamp recordings in combination with morphological and neurochemical analysis of VIP+ LM cells in acute slices obtained from VIP-Cre;Ai9 mice, we identified several distinct cell types. The majority of VIP+ LM cells had an axon projecting to the oriens/alveus with collaterals in the RAD. The second main population comprised VIP+ neurons that, in addition to innervating CA1, had projections to other cortical areas, including subiculum. The third type included VIP+ interneurons with local dense innervation of the CA1 LM and RAD. Unsupervised cluster analysis of membrane properties of VIP+ LM cells confirmed the existence of several cell types

with distinct action potential and firing properties, including the regularly-spiking, rapidly-adapting and irregularly-spiking cells. The majority of VIP+ LM cells co-expressed calretinin. Taken together, these data elucidate the structural and functional diversity within hippocampal VIP+ disinhibitory circuits, with different cell types likely playing distinct roles in hippocampal mnemonic processing and executive functions.

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Poster

466. Memory Systems

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Support: The National Centre of Research and Development (grant no 01.02.00-00-0023/17-001)

Title: Gap junction are involved in modulation of hippocampal theta rhythm induced by vagal nerve stimulation in anesthetized rats

Authors: *R. BOCIAN[1], A. BRONCEL[2], P. KŁOS-WOJTCZAK[2], J. KONOPACKI[1]; [1]Dept. of Neurobio., Univ. of Lodz, Lodz, Poland; [2]Res. Dept., Med. Technol. Ctr., Natolin, Poland

Abstract: INTRODUCTION: Vagal nerve stimulation (VNS) is currently approved for treatment of both pharmacologically resistant seizures and severe refractory depression. In addition, VNS is used for treatment of Alzheimer disease, schizophrenia and central inflammation. Interestingly, VNS has also been demonstrated to enhance long-term potentiation in the hippocampal formation (HPC) and improve memory in rats and humans. Just recently it was demonstrated that VNS is capable of inducing hippocampal theta rhythm (Broncel et al., 2017). The neuronal substrate underlying this novel phenomenon is poorly known. To note, the cholinergic and GABAergic profile of VNS-induced theta activity in anesthetized rats has just recently been addressed (Broncel et al., 2018, 2019). AIM: In a present study we extended our earlier observation concerning pharmacological profile of VNS-induced theta oscillations. Specifically, the purpose of the present study was to test the hypothesis that the VNS-induced hippocampal theta rhythm could be modulated by local HPC gap junctions (GJs) transmission. ANIMALS AND METHODS: Male Wistar rats were implanted with cuff stimulating electrode on left vagus nerve and tungsten recording electrode into HPC. The VNS was applied using following square pulse parameters: pulse duration 1 ms, train duration 10 s, frequency 10 Hz and a current intensity of 8 mA. These VNS parameters were previously found to induce a direct effect on HPC field potential i.e. theta rhythm appearing during vagal stimulation. Two GJs

agents carbenoxolon, the nonspecific GJs blocker and trimethylamine, the nonspecific opener of gap junction were injected into HPC. Two parameters (power and frequency) of VNS-induced theta rhythm were evaluated. RESULTS: It was demonstrated that carbenoxolone slowly inhibits VNS-induced theta while trimethylamine slowly facilities it. Injection of both agents evoked changes in VNS-induced theta power and were without any effects on frequency. CONCLUSIONS: These observations indicate that HPC electrical coupling mediates the theta rhythm induced by VNS.

Disclosures: R. Bocian: None. **A. Broncel:** None. **P. Kłos-Wojtczak:** None. **J. Konopacki:** None.

Poster

466. Memory Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 466.07/C20

Topic: B.09. Network interactions

Title: Validation of spiking sorting methods with paired recordings from awake mice

Authors: *L. M. F. KLAVER[1], R. C. BULLINS[1], K. C. ARNDT[1], E. GILBERT[1], M. FRICKE[1], P. HANNA[1], J. J. JUN[2], D. F. ENGLISH[1];
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Abstract: Extracellular single unit recording in behaving animals is rapidly increasing in popularity throughout the neuroscience community. The advent of large-scale devices, such as Neuropixels, in addition to existing silicon-probe and tetrode technologies, has led to more investigators using this method in an increasing array of behavioral setting and different brain areas. A critical step in the processing of data obtained with any of these devices is spike-sorting: the assignment of spikes to individual neurons. This process has evolved from largely manual cluster cutting methods to near-automated algorithms. While processing speed has increased dramatically, it is unknown whether the accuracy has followed a similar trajectory. A primary impediment to benchmarking the performance of any spike sorting method is the lack of ground-truth data. Such data consists of the same neuron(s) being recording with an unambiguous technique (i.e. juxtacellular or patch electrode) and an extracellular probe. To date there is a very limited set of such data, primarily obtained from a limited set of brain regions (hippocampus and neocortex) in anesthetized animals. There is a current need for high-quality, long-duration ground-truth recordings in multiple brain areas in awake animals.To generate a ground-truth dataset for spike sorting validation across multiple brain areas in awake mice, we developed a hybrid juxtacellular/silicon probe in which the glass electrode tip is positioned ~20 microns from the nearest silicon probe recording site. The proximity of these recording sites allows us to obtain an extracellular response of the juxtacellularly recorded unit with a sufficiently high signal-to-

noise ratio (SNR ranging from ~3-9). Preliminary data suggest that these devices produce stable recordings in multiple brain areas of awake, head-fixed mice for ~20-60 minutes. The combination of multiple brain areas, suitable recording length, and high SNR, in awake behaving mice, makes this dataset ideal for spike sorting validation. We will evaluate the performance of multiple spike sorting algorithms and determine their failure points relative to: population synchrony, bursting, spike waveform similarity and noise events including movement artifacts.To facilitate this process in a transparent and open-source manner, this project will be integrated into the SpikeForest framework, a public spike sorting evaluation website created and hosted by the Flatiron Institute.

Disclosures: L.M.F. Klaver: None. **R.C. Bullins:** None. **K.C. Arndt:** None. **E. Gilbert:** None. **M. Fricke:** None. **P. Hanna:** None. **J.J. Jun:** None. **D.F. English:** None.

Poster

466. Memory Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 466.08/C21

Topic: B.09. Network interactions

Title: Dynamics of glutamatergic transmission onto CA1 neurons in awake mice

Authors: *E. GILBERT[1], K. C. ARNDT[1], L. M. KLAVER[1], R. BULLINS[2], M. FRICKE[1], P. HANNA[1], D. F. ENGLISH[1];
[1]Sch. of Neurosci., [2]Virginia Tech., Blacksburg, VA

Abstract: Pyramidal neurons in hippocampus area CA1 receive excitatory glutamatergic afferent inputs from the entorhinal cortex and CA2/3, while interneurons additionally receive such inputs from local pyramidal neurons. During wakefulness, the hippocampus alternates between two states, each with identifiable correlates in the local field potential (LFP): active behaviors are accompanied by theta oscillations, while quiet wakefulness and consummatory behaviors are accompanied by large-irregular activity (LIA) in the LFP, including sharp-wave ripples (SWR). Excitatory inputs during both states are believed to shape these local field potential signatures. During theta oscillations, entorhinal and CA3 inputs arrive at distinct phases of theta, which is believed to support phase precession of place cells, while during LIA, CA2/3 glutamatergic input provides the excitatory drive to initiate SWRs. These findings have been primarily based upon analysis of single unit spiking across brain areas and corresponding LFP in hippocampal subfields and layers. While these measures have been invaluable in determining the functional relationships between these structures, they are insufficient to examine the dynamics of inputs to individual neurons across brain states.
To investigate the dynamics of excitatory inputs to identified single neurons in CA1 during different states, we are using an awake mouse preparation which combines local field potential

recording with two-photon imaging of extracellular glutamate. Local field potentials are recorded with standard methods, while glutamate is visualized using the genetically encoded glutamate sensor iGluSnFR *(1)*. As expected from known anatomy, during quiet wakefulness we observed coincident glutamate transients surrounding many dendritic shafts in the stratum radiatum layer, and less so surrounding somas in the pyramidal layer. Additional experiments will investigate the dynamics of these events in different cell types across multiple states and behaviors.
1. Marvin JS, Scholl B, Wilson DE, Podgorski K, Kazemipour A, Müller JA, Schoch S, Quiroz FJU, Rebola N, Bao H, Little JP, Tkachuk AN, Cai E, Hantman AW, Wang SS, DePiero VJ, Borghuis BG, Chapman ER, Dietrich D, DiGregorio DA, Fitzpatrick D, Looger LL. Stability, affinity, and chromatic variants of the glutamate sensor iGluSnFR. Nat Methods. 2018 Nov;15(11):936-939. doi: 10.1038/s41592-018-0171-3

Disclosures: **E. Gilbert:** None. **K.C. Arndt:** None. **L.M. Klaver:** None. **R. Bullins:** None. **M. Fricke:** None. **P. Hanna:** None. **D.F. English:** None.

Poster

466. Memory Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 466.09/C22

Topic: B.09. Network interactions

Title: Mechanisms of ripple oscillations in cortical regions

Authors: *K. C. ARNDT[1], L. M. KLAVER[1], E. GILBERT[1], M. FRICKE[1], R. BULLINS[1], P. HANNA[1], S. A. MCKENZIE[2], D. F. ENGLISH[1];
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Abstract: Sharp-wave associated ripple oscillations (~100-200 Hz) in the CA1 region of the hippocampus are a key component of hippocampal function *(1)*. Replay of place cell sequences occurs during ripples, and interruption of ripples during sleep and wakefulness impairs memory consolidation. The proposed significance of the speed of the ripple oscillation is to enable plasticity in downstream cortical targets, although ripple oscillations are not observed in most cortical areas. Recently, studies in rodents *(2)* and humans *(3)* have found restricted areas of cortex exhibiting ripple oscillations, temporally correlated to hippocampal ripples and related to learning.
The mechanisms of ripple oscillations in the hippocampus have been characterized at the synaptic and cellular level, and involve interactions between excitatory and inhibitory neurons, with inhibition setting the pace of the oscillation. Optogenetic stimulation of excitatory neurons in CA1, dentate gyrus and layer 5 of the somatosensory cortex has been demonstrated to evoke ripple-like oscillations, termed induced high frequency oscillations (iHFOs). This suggests that such oscillations may be an inherent property of circuits composed of excitatory and inhibitory

neurons, and that sufficient excitatory drive may evoke such oscillations in a variety of structures. Alternatively, different circuit architectures across cortical areas and layers may be more or less suited to supporting ripple generation, which may explain why ripples are not observed in all cortical areas and layers.
Using electrophysiological and optogenetic approaches in awake mice, we are investigating the ability for multiple cortical areas and layers to support ripple oscillations and iHFOs. Preliminary data suggests that in the retrosplenial cortex, a hippocampal target which exhibits ripple oscillations in layer 2/3, iHFOs may be preferentially generated in superficial layers. This would suggest that in addition to an excitatory drive of sufficient magnitude, the generation of ripple oscillations in extra-hippocampal cortical areas may also rely on specialized single cell physiology and/or local circuit interactions.
1. Buzsáki G. Hippocampal sharp wave-ripple: A cognitive biomarker for episodic memory and planning. Hippocampus. 2015 Oct;25(10):1073-188
2. Khodagholy D, Gelinas JN, Buzsáki G. Learning-enhanced coupling between ripple oscillations in association cortices and hippocampus. Science. 2017 Oct 20;358(6361):369-372
3. Vaz AP, Inati SK, Brunel N, Zaghloul KA. Coupled ripple oscillations between the medial temporal lobe and neocortex retrieve human memory. Science. 2019 Mar 1;363(6430):975-978

Disclosures: K.C. Arndt: None. **L.M. Klaver:** None. **E. Gilbert:** None. **M. Fricke:** None. **R. Bullins:** None. **P. Hanna:** None. **S.A. McKenzie:** None. **D.F. English:** None.

Poster

466. Memory Systems

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 466.10/C23

Topic: I.02. Systems Biology and Bioinformatics

Support: ISF Grant # 1928-2015
ONR #ON0014-18-2631

Title: First insight into the connectome of the octopus learning and memory system

Authors: *F. BIDEL[1], Y. MEIROVITCH[2], R. SCHALEK[2], X. LU[2], A. PELEG[2], T. FLASH[3], J. W. LICHTMAN[2], B. HOCHNER[1];
[1]Dept. of Neurobio., Hebrew Univ., Jerusalem, Israel; [2]NWL 249.50, Harvard Univ., Cambridge, MA; [3]Dept. of Computer Sci. and Applied Mathematics, Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Cephalopod molluscs like *Octopus vulgaris* have the most highly evolved nervous systems of any invertebrate group and exhibit sophisticated cognitive abilities which depend on a

pivotal brain structure: the vertical lobe (VL). The VL shows an anatomical connectivity organization typical of learning and memory network like the insect mushroom body and vertebrate hippocampus and cerebellum. However, previous anatomical considerations, supported by more recent physiological experiments have suggested that the VL is organized in a simple "fan-out fan-in" connectivity scheme with a robust NO-mediated LTP at the fan-out synaptic connections and a rich neuromodulation. More specifically, our current understanding of the VL circuitry and ultrastructure relies on the ground breaking work of J. Z. Young and E. G. Gray which suggests that ~ 1.8 million afferents from the medial superior frontal lobe are mediated to the ~ 60K large VL output neurons by a computationally thick intermediate and local layer of ~ 25 million small interneurons, called amacrine cells. The aim of this work is to get a better understanding of the function of the learning and memory circuitry of the octopus by producing the first detailed description of the synaptic and neuromodulatory connections of the various neurons comprising the VL, using recent progress of volume electron microscopy imaging. Accordingly, we collected and fixed *O. vulgaris* VL and subsequently serially sliced, imaged at 4 nm pixel resolution and aligned 1,000 30nm-sections from the VL using Automatic Tape-Collecting Lathe Ultramicrotome and a Scanning Electron Microscope (SEM). Extraordinary rich and highly dense synaptic profiles, with various type and combinations of synaptic vesicle types, are observed across the VL neuropil. Based on vesicles characteristics, filaments and organelles types and density, we have identified at least six different types of neuronal compartments in this circuitry. At least five categories of large repeating synaptic structures are found between those neuronal compartments, suggesting a possibly more elaborate circuitry than the one so far documented. Remarkably, whereas many of the synaptic categories we characterize are abundant in other invertebrates, at least one category shows greater similarity to a pyramidal spiny synapse. This work establishes the foundations for future connectomics work that will attempt to fully reconstruct the circuitry of the VL. We believe that a high-resolution connectome map of the VL will play a key role in understanding the network properties that have independently evolved in the complex learning and memory system of this advanced invertebrate.

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Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.01/C24

Topic: B.10. Epilepsy

Support: State Fund of Fundamental Research of Ukraine F74
Grant from Zayed University, Abu Dhabi, UAE.

Title: Protease-activated receptor 1 rescues impaired synaptic plasticity and anxiety-related behavior but does not affect spatial learning deficit in juvenile rat after status epilepticus

Authors: *O. ISAEVA[1], M. SEMENIKHINA[1], R. BOHOVYK[1], M. FEDORIUK[1], O. NIKOLAIENKO[1], L. T. ALKURY[2], A. SAVOTCHENKO[1], O. KRISHTAL[1];
[1]Bogomoletz Inst. of Physiol., Kiev, Ukraine; [2]Col. of Natural and Hlth. Sciences, Zayed Univ., Abu Dhabi, United Arab Emirates

Abstract: Brain injuries are often accompanied by the disruption of blood-brain barrier (BBB) integrity. Consequences of BBB dysfunction can greatly affect neuronal excitability and induce epileptic seizures. Inhibition of protease-activated receptor 1 (PAR1), a major thrombin receptor in the brain, produces an anti-epileptogenic and neuroprotective effects in an experimental model of temporal lobe epilepsy (TLE). Since serine proteases and PAR1 are implicated in the synaptic plasticity and memory formation, the aim of the present study was to evaluate the involvement of PAR1 in synaptic plasticity and behavior deficits following SE. Using lithium-pilocarpine model of TLE in juvenile rat, we demonstrate that inhibition of PAR1 rescues SE-induced synaptic plasticity deficits in CA1 region of hippocampus. Although treatment with PAR1 antagonist does not ameliorate spatial learning deficits, it attenuates an anxiolytic-like behavior in juvenile rats after SE. Taken together; our data suggest an important role of PAR1 in SE-induced synaptic and behavioral alterations and provide a new insight into the cellular mechanisms underlying behavioral impairments associated with epilepsy.

Disclosures: O. Isaeva: None. **M. Semenikhina:** None. **R. Bohovyk:** None. **M. Fedoriuk:** None. **O. Nikolaienko:** None. **L.T. AlKury:** None. **A. Savotchenko:** None. **O. Krishtal:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.02/C25

Topic: B.10. Epilepsy

Support: The EU-GliaPhD project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 722053.

Title: Impact of seizure activity on apoptosis and epileptogenesis in a guinea pig model of mesial temporal lobe epilepsy

Authors: *D. VILA VERDE, A. CATTALINI, F. COLCIAGHI, M. DE CURTIS;
Epilepsy Unit, Fondazione Inst. Neurologico "Carlo Besta", Milan, Italy

Abstract: Seizures are observed in several neurological disorders and are associated with social stigma and co-morbidities. Sustained seizure activity is thought to be responsible for altering both neuronal and glial function, thus influencing the process of epileptogenesis and ictogenesis. This has not been definitively demonstrated since seizures and brain damage develop in parallel in many epilepsies. The present study aims to evaluate if seizure activity *per se* could be sufficient to induce the expression of brain damage biomarkers and consequently worsening of epileptogenesis. To achieve this, we used an animal model in which focal non-convulsive status epilepticus (ncSE) was evoked in guinea pigs by unilateral injection of kainic acid (KA) in the hippocampus (Hpc) with continuous video-EEG recording for 3 days (n=10). Moreover, to differentiate the effects of KA alone, another group was added, in which KA-injected animals were treated with diazepam (DZP, n=5) which markedly reduce seizures during SE. KA animals exhibited a non-convulsive SE with seizures lasting from 6 up to 12 hours. The advantage of this model is to have a contra-lateral Hpc that has as much seizures as the ipsi-lateral side, but without the cytotoxic effects of KA and, in fact, 57,3 ± 4,2 % of all seizures were focal but bilateral. Immunohistochemical analysis on neuronal markers NeuN and MAP2, Tunel and Fluoro-Jade (FJ) showed a significant reduction in the number of neurons in the Hpc (n=8) ipsi-lateral to KA injection, compared to sham controls (n=6) in CA1/CA3; with DZP this reduction was less severe. In the Hpc contra-lateral to KA injection, no reduction of neurons was found in sham, KA- and DZP-injected animals. In KA-injected animals, the ipsi-lateral Hpc had a significant increase in Tunel and FJ positive cells, compared to controls and the contra-lateral side. DZP-treated animals showed a statistical increase in the ipsi-lateral Hpc compared to controls but not as incremented as the KA-injected animals. As expected, injecting KA induced neuronal death in the ipsi-lateral Hpc in CA1 and CA3. When animals were administered with DZP this damage was still present but in a less aggressive fashion. This suggests a possible synergy between KA and seizures to induce apoptosis and cell loss. However, we observed that seizures *per se* were not sufficient to induce neuronal death. These findings hint to the possibility that seizures are not responsible for inducing brain damage through apoptosis, but coupled with a previous insult (trauma, infection, etc) they may exacerbate the effect of the preceding malady.

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Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.03/C26

Topic: B.10. Epilepsy

Support: NIH/NINDS R01NS095042
University of Iowa Graduate College Post-Comprehensive Research Fellowship

NIH/NINDS F31 NS106819-01
Beth L. Tross Epilepsy Professorship

Title: Circadian rhythmicity in vulnerability to seizure induced death

Authors: *B. S. PURNELL[1], G. F. BUCHANAN[2];
[2]Neurol., [1]Univ. of Iowa, Iowa City, IA

Abstract: Over 50 million people worldwide live with epilepsy. The leading cause of epilepsy related death is sudden unexpected death in epilepsy (SUDEP). More years of potential life are lost to SUDEP than any other neurological disease with the exception of stroke. There is a great deal which is not known about SUDEP; there are no known ways of preventing it, predicting when it will happen, or identifying patients at the greatest risk. What is known is that SUDEP typically happens during the night following some form of seizure-induced cardiorespiratory failure. Many aspects of mammalian physiology and behavior are subject to regulation by circadian rhythmicity in ways that might make seizures that occur during the night more dangerous. The goal of this investigation was to test the hypothesis that circadian rhythmicity alters vulnerability to seizure induced death. Our approach was to induce seizures at different circadian phases and monitor seizure severity, mortality, and respiratory sequelae. Male C57BL/6J mice (7-10 weeks old) were singly housed in cages equipped with running wheels in a 12:12 light-dark schedule and allowed to entrain normally to the ambient lighting conditions for 7-10 days. Mice were then housed in conditions of constant darkness (DD) until their free-running period could be easily determined using running wheel activity. Maximal electroshock seizures were induced at six circadian time points (circadian time [CT] 2, 6, 10, 14, 18, and 22. n = 9 per time point). Seizures were monitored using infrared video for quantification of motor seizure severity. Whole body plethysmography was recorded before during and after the seizure to quantify the respiratory outcome of the seizure. We found that seizure induced death was not uniformly distributed across the experimental time points with an increased rate towards the end of the subjective night ($p = 0.04$, V test for circular uniformity). These results indicate that circadian rhythmicity alters vulnerability to seizure induced death. Circadian differences in vulnerability to seizure induced death may contribute to the increased nocturnal incidence of SUDEP. Future investigations into the mechanistic underpinnings responsible for circadian differences in vulnerability to seizure induced death may inform the development of preventative strategies for SUDEP.

Disclosures: B.S. Purnell: None. **G.F. Buchanan:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.04/C27

Topic: B.10. Epilepsy

Support: NIH/NINDS R01NS095842
Beth L. Tross Epilepsy Professorship
University of Iowa Post-Comprehensive Exam Fellowship

Title: Stimulation of DRN serotonin neurons decreases PGES length and reduces seizure-induced mortality

Authors: *A. N. PETRUCCI[1], J. CHOU[1], K. VENCER[2], G. F. BUCHANAN[1];
[1]Dept. of Neurol., [2]Dept. of Hlth. and Human Physiol., Univ. of Iowa, Iowa City, IA

Abstract: Sudden unexpected death in epilepsy (SUDEP) is the leading cause of death in individuals with uncontrolled epilepsy. The exact etiology of SUDEP is unknown. A potential risk marker for SUDEP is post-ictal generalized EEG suppression (PGES), a period of low amplitude EEG activity following some seizures. The cause of PGES is unknown, but PGES duration may correlate with SUDEP risk. Our lab has demonstrated that PGES can occur after maximal electroshock (MES) and kindled seizures in mice and that pharmacologically increasing 5-HT tone reduces PGES duration. We hypothesized that the dorsal raphe nucleus (DRN) may be involved in PGES. The DRN sends 5-HT projections broadly to regions associated with arousal and its firing is reduced by seizures. Therefore, stimulating the DRN may reduce PGES duration and mortality. Six C57BL/6J (3 male/3 female; 8-12 weeks old) and eight *Pet1-Cre* and WT mice (4 male/4 female per genotype; 8-12 weeks old) were implanted with EEG and EMG electrodes and a bipolar stimulating/recording electrode in the right basolateral amygdala (AP: -1.3 mm; ML: -2.8 mm; DV: -4.7 mm). C57BL/6J mice were additionally instrumented with a microdialysis cannula directed toward the DRN (AP: -4.6 mm; ML: 0 mm; DV: -3.0 mm) and *Pet1-Cre*/WT mice received a microinjection (500 nl) of AAV-ChR2 and implantation of a fiberoptic cannula into the DRN. After recovery, afterdischarge threshold determination, and kindling, animals underwent seizure inductions (120-500 µA, 1 sec train of 1 msec square wave pulses at 60 Hz) during wake or sleep following focal chemical (45 µl/min, 6.8 pH artificial cerebrospinal fluid, 10 min) or optogenetic (473 nm, 4 Hz, 10 mW, 2% duty, 10 s ON / 10 s OFF, 10 min) DRN stimulation. Seizure severity and PGES duration was assessed. In a separate set of experiments, twelve (5 male, 7 female; 8-12 weeks old) C57BL/6J mice were implanted with EEG/EMG electrodes and a microdialysis cannula into the DRN. Mice underwent seizure induction via MES (60 mA, 0.2 s, 60 Hz sine wave pulses) following chemical DRN stimulation as above. Mortality, seizure duration, and seizure severity were determined off-line by post hoc video review. After experimentation, animals were intracardially perfused and implant placements were verified histologically. Pre-seizure focal chemical and optogenetic stimulation of the DRN decreased PGES length. Identical chemical DRN stimulation reduced mortality in the MES model. These data suggest that the DRN may be implicated in PGES generation and in seizure-induced mortality. In the future we will determine the downstream circuitry and 5-HT receptor subtypes underlying the effect of DRN stimulation on PGES generation.

Disclosures: A.N. Petrucci: None. **J. Chou:** None. **K. Vencer:** None. **G.F. Buchanan:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.05/C28

Topic: B.10. Epilepsy

Support: NINDS grant NS090076
Postdoctoral research fellowship from the American Epilepsy Society

Title: Gabapentin treatment reduces status epilepticus-induced neocortical injury

Authors: *M. B. PEREZ-RAMIREZ[1], I. PARADA[2], R. MOEIN[2], D. A. PRINCE[3];
[1]Neurol. and Neurolog. Sci., [2]Stanford Univ., Palo Alto, CA; [3]Stanford Hosp. and Clinics, Stanford, CA

Abstract: Status epilepticus (SE) is a seizure that can last more than 5 minutes and it increases the probability for subsequent seizures. For instance, prolonged febrile seizures in children, are associated with a risk of subsequent temporal lobe epilepsy. The mechanisms by which neocortical SE induces chronic sequella, including epileptogenesis, are not yet fully understood. Furthermore, there is no available therapy to prevent epileptogenesis or other morbidities following SE. Gabapentin is an antiallodynic and anticonvulsant drug known to inhibit the interaction between TSPs and α2δ-1, and it is also known to have anti-synaptogenic effects. We focus on studying focal neocortical seizures to understand what types of potentially epileptogenic chronic synaptic changes may occur following 10 and 30 days of a single episode of SE in the neocortex and whether or not gabapentin can rescue the abnormalities following SE. In the present study we use immunohistochemistry (ICC) and electrophisiology techniques, to assess structural and functional changes after a focal episode of SE, and Gabapentin treatment to prevent these changes. Our results show increased immunoreactivity for putative excitatory synapses and for astrocytic proteins. Additionally, SE provoked abnormal local field potentials and increased miniature excitatory postsynaptic currents (mEPSCs) in the affected neocortex. Gabapentin can reduce the increased excitatory connections as well as decrease the astrocytic proteins. Further studies need to be done to address the gabapentin effects on the functional modifications.

Disclosures: **M.B. Perez-Ramirez:** None. **I. Parada:** None. **R. Moein:** None. **D.A. Prince:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.06/C29

Topic: B.10. Epilepsy

Support: NSF Grant No. 1315232
NIH T32GM007518

Title: Changes in the homeostatic roles of microglia induced by cannabidiol (CBD) in a translational model of epilepsy

Authors: *T. R. VICTOR[1], M. W. ELMES[2], D. G. DEUTSCH[2], S. E. TSIRKA[1];
[1]Mol. and Cell. Pharmacol., [2]Biochem. and Cell Biol., Stony Brook Univ., Stony Brook, NY

Abstract: Epilepsy is a chronic neurological disorder due to abnormal activity in neuronal circuits and characterized by repeated seizures. It affects 1% of people worldwide and considerably impacts the quality of life of both patients and caregivers. There are currently over 25 anti-epileptic drugs (AEDs) available, however these drugs only relieve seizure symptoms and can have severe adverse effects. Even with the variety of AED's available, approximately one-third of patients with epilepsy are unresponsive to the available drugs. Cannabidiol (CBD), a non-psychotropic component of *Cannabis sativa,* was recently approved by the FDA for use for intractable epilepsies, and provides a well-tolerated therapeutic option for those who do not respond to traditional AEDs. CBD has neuroprotective properties and lessens the severity of experimentally induced seizures in animals and suppresses neuroinflammation in culture. While effective, the mechanism CBD utilizes to achieve its anti-epileptic effects is still poorly understood. Our lab has shown that microglia, the immune cells of the central nervous system (CNS), act as important mediators of seizure severity. We postulate that CBD exerts positive effects that affect microglial roles. Our data suggest that CBD is effective as a therapeutic agent in a kainate model of induced epilepsy. Administered late after the onset of seizures, it suppresses successive seizure events and modulates microglial activation. This study evaluates the effects of CBD on microglia-mediated processes, which include inflammation, apoptosis, and neurogenesis post seizure. The results of this study will provide insights the mechanism of CBD action and help identify potential targets for the future medications that can aid in the optimal performance of neuronal circuits. This work was partially supported by an NSF Predoctoral Fellowship and SBMS funds to TRV.

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Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.07/C30

Topic: B.10. Epilepsy

Support: FAPESP 2016/22447-5

Title: Transcriptome investigation of the mechanisms involved in preconditioning induced by electrical stimulation of the perforant pathway in the rat

Authors: G. G. ZANETTI[1], E. V. DIAS[2], I. LOPES-CENDES[1], ***A. S. VIEIRA**[3];
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Abstract: The most frequent neuroimage finding in mesial temporal lobe epilepsy (MTLE) patients is Mesial Temporal Sclerosis, that has hippocampal atrophy as one of its main components. The electrical stimulation of the perforant pathway for a period of 8 hours in awake rats reproduces hippocampal lesion with a morphology that resembles the human condition without the induction of an episode of status epilepticus (SE). In order for animals to survive such a long period of stimulation in this model it is necessary two days of 30 minutes preconditioning sessions by electrical stimulation of the perforant pathway. Therefore, the objective of the present study is to explore the biological processes, and the molecular components involved in the preconditioning of the hippocampus employing transcriptomic analysis of the different hippocampal sub-regions.Electrodes were implanted bilaterally in the dentate girus (DG) and in PP of control (n=5) and experimental rats (n=5). After one week the PP of experimental rats were electrically stimulated for 30 minutes in two subsequent days. 24h following stimulation rats were euthanized and the brains processed for laser microdissected using Zeiss PALM LCM. Dorsal (dDG) and Ventral DG (vDG) were collected from each rat, total RNA was extracted, and libraries for RNAseq in Illumina Hiseq platform were prepared. A total of 1,895 genes were differentially expressed ($p<0,05$) when comparing the control Dentate Gyrus with the stimulated Dentate Gyrus, 908 genes were at the Dorsal region (DDG) and 459 were ventral region (VDG), and 528 genes at both regions. Pathway enrichment analysis indicated that both DDG and VDG presented differently expression genes related with inhibitory pathway, showing up regulation with GABAA receptors, GABA biosynthesis, and down regulation of genes in cAMP pathway and GAT, indicating a coordinated increase of inhibition. The cholesterol biosynthesis pathway was up-regulated exclusively in VDG. The transcriptome data explored in this study suggest different functions depending the region of Dentate Gyrus. The transcriptome data also indicates a marked increase in inhibition in the DG after pre-conditioning, a observation consistent with previous physiological data.

Disclosures: **G.G. Zanetti:** None. **I. Lopes-Cendes:** None. **A.S. Vieira:** None. **E.V. Dias:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.08/C31

Topic: B.10. Epilepsy

Support: NINDS 056217
CURE Taking Flight Award
Predoctoral Research Fellowship (American Epilepsy Society)

Title: TrkB-Shc signaling protects against hippocampal injury following status epilepticus

Authors: Y. Z. HUANG[1], X.-P. XIAO[1], K. KRISHNAMURTHY[1], ***J. O. MCNAMARA**[2]; [1]Dept. of Neurobio., [2]Dept. of Neurobiology, Med. (Neurology), Pharmacol. and Mol. Cancer Biol., Duke Univ. Med. Ctr., Durham, NC

Abstract: Temporal lobe epilepsy (TLE) is a common and commonly devastating form of human epilepsy for which only symptomatic therapy is available. One cause of TLE is an episode of *de novo* prolonged seizures (status epilepticus, SE). Understanding the molecular signaling mechanisms by which SE transforms a brain from normal to epileptic may reveal novel targets for preventive and disease-modifying therapies. SE-induced activation of the BDNF receptor tyrosine kinase, TrkB, is one signaling pathway by which SE induces TLE. While activation of TrkB signaling promotes development of epilepsy in this context, it also reduces SE-induced neuronal death. This led us to hypothesize that distinct signaling pathways downstream of TrkB mediate the desirable (neuroprotective) and undesirable (epileptogenesis) consequences. We subsequently demonstrated that TrkB-mediated activation of PLCγ1 is required for epileptogenesis. Here we tested the hypothesis that the TrkB-Shc-Akt signaling pathway mediates the neuroprotective consequences of TrkB activation following SE. We studied measures of molecular signaling and cell death in a model of SE in mice of both sexes, including wild-type and *TrkB*$^{Shc/Shc}$ mutant mice in which a point mutation (Y515F) of TrkB prevents the binding of Shc to activated TrkB kinase. Genetic disruption of TrkB-Shc signaling had no effect on severity of SE yet partially inhibited activation of the pro-survival adaptor protein Akt. Importantly, genetic disruption of TrkB-Shc signaling exacerbated hippocampal neuronal death induced by SE. We conclude that that therapies targeting TrkB signaling for preventing epilepsy should spare TrkB-Shc-Akt signaling and thereby preserve the neuroprotective benefits.

Disclosures: **Y.Z. Huang:** None. **X. Xiao:** None. **K. Krishnamurthy:** None. **J.O. McNamara:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.09/C32

Topic: B.10. Epilepsy

Support: R56/RO1 Grant NS096234

Title: The status of immune complement cascade activation in epilepsy

Authors: A. L. SOMMER[1], N. D. SCHARTZ[2], A. AROOR[1], *A. L. BREWSTER[1];
[2]Psychological Sci., [1]Purdue Univ., West Lafayette, IN

Abstract: Individuals with refractory epilepsy have drug-resistant seizures. Surgical resection of the seizure focal point is often the preferred remaining treatment option for refractory epilepsy, but not all patients are candidates. Thus, our objective is to identify novel therapeutic targets for drug-resistant epilepsy focusing on signaling cascades that modulate neuroimmune interactions such as the classical complement pathway (C1q-C3) of the immune complement system. Histopathological features of drug-resistant epilepsy include a decline in synaptodendritic elements and neurons, along with microgliosis. Through characterizations of brain samples derived from human refractory epilepsy we previously reported alterations in complement proteins C1q and C3 (Wyatt et al. Experimental Neurology. 2017; 295:184-193). These proteins are associated with the regulation of inflammatory and phagocytic responses, as well as microglial synaptic pruning in the developing brain and in neurodegenerative disorders. In this study we investigated the status of immune complement activation by determining the extent to which C1q and C3 signaling is associated with the downstream activation of C5 in a large pool of brain samples from patients with refractory epilepsy (n=17). Because complement C3 is linked to synaptic loss of PSD95, we determined the correlation between complement and PSD95 levels within the same samples.
Western blots (WB) with antibodies against C1q, C3, C5, and PSD95 were done in whole tissue homogenates containing a mix of gray and white matter.
Results from the WBs showed a correlation between the protein levels of C3 and C5 ($p<0.0001$), as well as between C3 and PSD95 ($p=0.076$) within the samples. However, there was no significant correlation between proteins C1q and C5 ($p=0.1085$) or between C1q and C3 ($p=0.5165$).
Based on these results, we speculate that the significant correlation between levels of complement proteins C3 and PSD95 may indicate a close association complement activation and

synaptic remodeling in epilepsy. Mechanistic studies are currently underway to determine the role of complement proteins in pathological synaptic remodeling in epilepsy.

Disclosures: A.L. Brewster: None. **A.L. Sommer:** None. **N.D. Schartz:** None. **A. Aroor:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: B.10. Epilepsy

Support: NIH Grant 1R01NS096234-01A1
Purdue Research Foundation Grant

Title: A role for microgliosis in the neuropathology of prolonged seizures

Authors: *S. K. JOHNSON, A. L. SOMMER, S. LAM, A. L. BREWSTER;
Psychological Sci., Purdue Univ., West Lafayette, IN

Abstract: Evidence from experimental models of epilepsy support that prolonged seizures (status epilepticus, SE) promote pathological hippocampal synaptodendritic remodeling that contributes to the development of unprovoked seizures and cognitive decline. One potential mechanism underling the SE-induced sequelae is proliferation and activation of microglia (microgliosis). Previously we reported that inhibition of SE-induced microgliosis with rapamycin attenuated the loss of the dendritic protein Map2 in the hippocampus, as well as the associated hippocampal-dependent spatial learning and memory deficits (Brewster et al. PLoS One. 2013; 8(3):e57808). To further investigate the role of microgliosis in the SE-induced synaptodendritic pathology we tested the efficacy of a more selective inhibitor of microglia, PLX3397 (PLX), in our experimental model of epilepsy. PLX binds to colony stimulating factor 1 receptor on microglia and inhibits the downstream signaling responsible for survival and proliferation.
The pilocarpine model of SE was used to generate epileptic male rats. Those that reached seizure level 6 in the Racine scale were used for this study (n=8-11 per group). SE was induced with pilocarpine (1hr) and controls were given saline. PLX (50mg/kg in chow) or Vehicle (Veh; regular chow) were given immediately after SE for up to 3 weeks. Brains were processed for immunohistochemistry using antibodies against IBA1 to determine levels of hippocampal microgliosis. Four groups were evaluated: Control+Veh (n=9), SE+Veh (n=8), Control+PLX (n=6), and SE+PLX (n=11). Microglia were counted in 40x images, from 6 sections per animal. First we found that the PLX treatment significantly decreased microgliosis in Control+PLX rats compared to Control+Veh rats ($p<0.0001$; t-test). As expected, we found a significant increase in the number of microglial cells in hippocampi of SE+Veh rats compared to Control+Veh rats

($p<0.0001$; two-way ANOVA). Interestingly, in the PLX-treated SE group we observed two distinctive groups which we categorized as responders and non-responders when compared to the SE+Veh group. The SE+PLX responders (n=8) had significantly decreased microgliosis compared to the SE+Veh group ($p<0.0001$; two-way ANOVA). The SE+PLX nonresponses (n=3) had higher levels of microgliosis compared to the SE+Veh group ($p<0.0001$; two-way ANOVA).
These data indicate that PLX treatment suppresses microgliosis in our control and SE groups. Our findings support that PLX may be a useful tool to study whether suppression of microgliosis attenuates the synaptodendritic and cognitive decline following SE. Ongoing studies are testing this hypothesis.

Disclosures: S.K. Johnson: None. **A.L. Sommer:** None. **S. Lam:** None. **A.L. Brewster:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

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Program #/Poster #: 467.11/C34

Topic: B.10. Epilepsy

Support: NIH Grant 1R01NS096234-01A1
Purdue Research Foundation Research Grant

Title: Inhibition of complement C3 activation attenuates pathological cognitive and synaptic changes in a rat model of status epilepticus

Authors: *N. D. SCHARTZ[1], A. L. BREWSTER[2];
[2]Psychological Sci., [1]Purdue Univ., West Lafayette, IN

Abstract: Epilepsy is characterized by spontaneous recurrent seizures and comorbid conditions such as cognitive dysfunctions. In individuals with epilepsy, this pathophysiology can be exacerbated by episodes of prolonged continuous seizure activity (status epilepticus; SE). In an otherwise healthy system, SE provoked by adverse events including head trauma or stroke results in hippocampal injury and an increased risk for the subsequent development of epilepsy and cognitive decline. We previously reported that this pathophysiology correlates with SE-induced hippocampal dendritic instability, microgliosis, and complement C3 hyperactivation in both human and experimental epilepsy. Thus, in this study we tested the hypothesis that C3 inhibition after SE will attenuate memory deficits and synaptic protein loss in the hippocampus.
To eliminate C3 in rats we used the complement C3 inhibitor cobra venom factor (CVF). Male rats were injected with pilocarpine (300mg/g, i.p.) to induce SE or with saline (controls). Behavioral seizure severity to levels 5-6 (SE) was scored using the Racine scale. One week after SE, rats were injected with CVF (100ng/g, i.p.) or equal volume saline. Four groups were

investigated: Veh-C, Veh-SE, CVF-C, CVF-SE. Two weeks after SE, the novel object recognition (NOR) test was used to assess recognition memory. After NOR, hippocampi were processed for western blot with antibodies against the synaptic proteins PSD95 and VGat.
In the NOR test trial, rats from the Veh-C and CVF-C groups spent significantly more time exploring the novel object compared to the familiar object ($p<0.05$). In contrast, rats from the Veh-SE group spent a similar amount of time exploring both objects ($p=0.09$) while the CVF-SE rats spent significantly more time exploring the novel object ($p<0.001$), suggesting improved memory in the CVF-SE rats. After NOR, protein levels of PSD95 and VGat were determined in the hippocampus. We found a significant reduction in the protein levels of PSD95 ($p<0.01$) and Vgat ($p=0.04$) in the Veh-SE compared to Veh-C. However, there was no difference in PSD95 ($p=0.33$) or Vgat ($p=0.67$) between CVF-C and CVF-SE groups, suggesting that CVF attenuates the SE-induced loss of these synaptic proteins.
Taken together, these findings support that SE-induced C3 activation contributes to hippocampal synaptic remodeling and impairments in memory, and suggest that C3 may be a therapeutic target for the treatment of some memory deficits in epilepsy.

Disclosures: N.D. Schartz: None. **A.L. Brewster:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.12/C35

Topic: B.10. Epilepsy

Support: NIH Grant NS092760

Title: Noise assisted memd based phase connectivity analysis to personalize closed-loop DBS therapy in epilepsy patients

Authors: S. FARAHMAND[1], ***T. SOBAYO**[2], D. J. MOGUL[2];
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Abstract: Deep brain stimulation (DBS) is a treatment that has been explored for controlling seizures in patients with intractable epilepsy. Many clinical and pre-clinical studies using DBS therapy determine stimulation parameters through trial and error. The same stimulation parameters are often applied to the whole cohort, which consequently produces mixed results of responders and non-responders. In this study, an adaptive non-linear analytical methodology is proposed to extract stimulation frequency and location(s) from endogenous brain dynamics of epilepsy patients, using phase-synchrony and phase-connectivity analysis, as seizures evolve. The proposed method was applied to seizures recorded using depth electrodes implanted in both

hippocampus and amygdala in three patients. A reduction in phase-synchrony was observed in all patients around seizure onset. However, phase-synchrony started to gradually increase from mid-ictal and achieved its maximum level at seizure termination. This result suggests that hyper-synchronization of the epileptic network may be a crucial mechanism by which the brain naturally terminates seizure. Stimulation frequency and locations that matched the network phase-synchrony at seizure termination were extracted using phase-connectivity analysis. One patient with temporal lobe epilepsy (TLE) had a stimulation frequency ~15 Hz with the stimulation locations confined to the hippocampus. Another two patients with extra-temporal lobe epilepsy (ETE) had stimulation frequency ~90 Hz with at least one stimulation location outside of the hippocampus. These results suggest that DBS parameters may vary based on the patient's underlying pathology. The proposed methodology provides an algorithm for tuning DBS parameters for individual patients in an effort to increase the clinical efficacy of this therapy.

Disclosures: S. Farahmand: None. **T. Sobayo:** None. **D.J. Mogul:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

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Program #/Poster #: 467.13/C36

Topic: B.10. Epilepsy

Title: Examination of the association of bilateral language dominance with verbal learning/memory and language performance in patients with epilepsy

Authors: M. BERGER-NAGELE[1], M. KOLESSAR[1], K. C. BAILEY[2], T. O'NEILL[3], ***Z. F. YETKIN**[3];
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Abstract: Objective: Atypical language laterality, secondary to refractory epilepsy, presents complications to surgical planning and cognitive outcomes. The present study examined relationships between 1) the differences in language representation between mesial temporal sclerosis (MTS) and non-lesional epilepsy and 2) language laterality, as determined through functional Magnetic Resonance Imaging (fMRI), and performance on single trial learning and delayed memory (California Verbal Memory Test 2nd-edition (CVLT) and Rey Auditory Verbal Learning Test (RAVLT), phonemic verbal fluency (Controlled Oral Word Association Test (COWAT), and confrontation naming (Boston Naming Test 2nd Edition, BNT) in a sample of patients with intractable epilepsy.
Methods: Retrospective data was compiled on patients with refractory epilepsy undergoing interdisciplinary pre-surgical workup (N=101) with mean age of 37.2 (SD=11.9) and education of 12.3 (SD=3.7). The sample was then stratified by non-lesional (n=48) and mesial temporal

sclerosis (n=53). Language dominance as determined by voxelwise analysis of task-based functional MRI was stratified as unilateral, mixed bilateral, and pure bilateral.
Results: Analyses showed greater bilateral language dominance, as determined through fMRI, was negatively correlated with single trial learning on CVLT and RAVLT (rs = -0.45, p = 0.048) in patients with mesial temporal sclerosis (MTS); whereas no significance was found in non-lesional patients. No significant correlations were found across memory or language measures irrespective of lesional status.
Conclusions: Individuals with non-lesional epilepsy, demonstrated no significant association between bilateral language dominance and performance on cognitive measures. Patients with MTS and bilateral language dominance evidenced reduced performance on single trial verbal learning. Interestingly, the non-lesional epilepsy patients demonstrated an almost identical base rate of bilateral language dominance as compared to the patients with MTS. Therefore, these findings demonstrate the need for further examination of the interaction of atypical language dominance and lesional status in patients with epilepsy.

Disclosures: **M. Berger-Nagele:** None. **M. Kolessar:** None. **K.C. Bailey:** None. **T. O'Neill:** None. **Z.F. Yetkin:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

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Program #/Poster #: 467.14/C37

Topic: B.10. Epilepsy

Support: NIH Grant NS065877
NIH Grant NS033310
NIH Grant NS106957
NIH Grant NS100064

Title: Alterations of resting state functional brain connectivity in the early period of epileptogenesis - An EEG-fMRI combined study

Authors: L. LI[1], L. HE[3], C. BOU KHALIL[1], H. YEH[1], J. STERN[1], N. G. HARRIS[4], R. STABA[1], J. ENGEL, Jr.[1,2], *A. BRAGIN[1];
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Abstract: The current study aims to investigate the alterations of resting-state functional brain connectivity (rsFC) during an early period of epileptogenesis using combined EEG and fMRI modalities. Sprague-Dawley rats were injected with kainic acid in the left CA3 area to induce

status epilepticus (SE). One week before and 2 weeks after SE, 10 minutes of BOLD data were acquired using a single-shot, gradient-echo, echo-planar, fMRI sequence (TR/TE=2000, 35ms with voxel sizes of 0.27×0.27×0.75mm) from rats under a bolus of medetomidine sedation (0.5 mL / 0.1mg/kg). We performed an independent component analysis to identify the resting-state networks (RSNs), and to guide the selection of regions-of-interest (ROIs) for electrode implantation. As a result, a total 16 bilateral ROIs representing the key structures of RSNs were selected. After the second fMRI session at 2 weeks post-SE, depth electrodes were implanted in the ROIs including left/right Prelimbic cortex, left/right Anterior Cingular cortex, left/right Motor cortex and left/right Dorsal/Ventral Hippocampus. Wide-band electrical activity was recorded continuously for 8 weeks. A total 9 sham control rats and 12 rats that later develop spontaneous epilepsy (E+) were selected for a combinatorial analysis of fMRI and EEG data. Our results demonstrated (a), the BOLD-rsFC was stable across a one-week window period in both sham and E+ rats; (b) compared to the sham rats, increase of the intra-network connectivity and decreased of the inter-network connectivity was observed in the E+ rats**;** (c) pairs of ROIs with increased rsFC were associated with stronger EEG coupling (70-170Hz) and increased synchrony of multiunit discharges. These results suggest after an epileptogenic injury regional network dysregulation could produce local areas containing abnormal FC and hyperexcitability that support the development of epilepsy. Future work will investigate whether sites of increased BOLD rsFC correspond with pathological HFOs, which could provide a non-invasive approach to study the formation of PIN clusters during epileptogenesis.

Disclosures: L. Li: None. **L. He:** None. **C. Bou Khalil:** None. **H. Yeh:** None. **J. Stern:** None. **N.G. Harris:** None. **R. Staba:** None. **J. Engel:** None. **A. Bragin:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.15/C38

Topic: B.10. Epilepsy

Support: Politec Health

Title: Minimum spanning tree characteristics of refractory epilepsy patients

Authors: J. FIEL[1], E. M. MELO[1], R. NAVEGANTES[1], F. L. GOMES[2], ***A. PEREIRA**[3]; [1]Federal Univ. of Pará, Belém, Brazil; [2]Ophir Loyola Hosp., Belém, Brazil; [3]Federal Univ. of Pará/Institute of Technol., Belém, Brazil

Abstract: Network analysis has been successfully used to describe the topological and spatial organization of the human connectome. In the present work, we combined two approaches, the debiased weighted phase-lag index (dWPLI) and the minimum spanning tree (MST), to compare

the EEG functional connectivity network of refractory epilepsy (RE) patients and healthy subjects. The MST is considered being an unbiased method that allows a common frame of reference to compare brain networks. We recorded nine minutes of resting-state EEG from patients diagnosed with RE (N=7) and from sex- and age-matched healthy control participants (N=7). Functional Connectivity (FC) between pairs of electrodes was estimated with the dWPLI method and based on four frequency ranges: theta (4-8Hz), alpha (8-12Hz), beta (13-30Hz), and Low gamma (30-45Hz). We calculated a connectivity matrix for each subject and for each frequency range. Subsequently, the minimum spanning tree (MST) was measured in order to obtain the fundamental network properties. The normalized leaf fraction characterized the MSTs. We also calculated kappa value to get the degree distribution and thus the resilience to attacks against the network. We found key differences in network topology between the two experimental groups, specifically both the leaf fraction and divergence of resting state networks were notably larger in the RE group. These results suggest the MST organization of the RE patients presents a more random organization in comparison with the controls. Deviation towards randomization implies a suboptimal resting-state network organization of RE patients, which undermines the efficiency of information exchange across different brain regions

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Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

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Topic: B.10. Epilepsy

Support: CURE Taking Flight Award
Finding A Cure for Epilepsy and Seizures (FACES)

Title: Interictal epileptiform discharges shape large-scale intercortical communication

Authors: ***P. DAHAL**[1], N. GHANI[2], A. FLINKER[3], P. DUGAN[4], D. FRIEDMAN[4], W. DOYLE[4], O. DEVINSKY[4], D. KHODAGHOLY[1], J. GELINAS[2];
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Abstract: Dynamic interactions between remote but functionally specialized brain regions enable complex information processing. This intercortical communication is disrupted in the neural networks of patients with focal epilepsy, and epileptic activity can exert widespread effects within the brain. However, the mechanisms by which epileptic activity shapes large-scale

neural networks remain mostly unknown, and have broad implications for understanding coordination of distributed network activity in the human brain. Using large-scale human intracranial electroencephalography (iEEG) recordings, we have determined that interictal epileptiform activity in the human brain affects large-scale cortical networks through establishment of dynamic, pathologic oscillatory coupling. We show that interictal epileptiform discharges (IEDs) are significantly coupled with spindles in discrete, individualized brain regions outside of the epileptic network, establishing communication between the conventionally defined epileptic network and the rest of the brain. We ascertained that a substantial proportion of these localized spindles travel across the cortical surface, a property that has not previously been demonstrated for these oscillations. Brain regions that participate in this IED-driven oscillatory coupling express spindles that have a broader spatial extent and higher tendency to propagate than spindles occurring in uncoupled regions. These altered spatiotemporal oscillatory properties could identify areas at risk for recruitment into the epileptic network independent of IED or seizure detection. Our findings have key implications for understanding how dynamic oscillatory coupling can be established in the human brain, specifically focusing on how focal neural patterns can modulate properties of large-scale cortical networks. Furthermore, we hypothesize that these IED-driven, spatiotemporally specific patterns of abnormally coordinated brain activity could provide a mechanism for large-scale disruption of neural network function in focal epilepsy. Such patterns could contribute to impairment of processes that heavily rely upon intercortical communication, such as cognition and memory. Consequently, this coupling may represent a therapeutic target for closed-loop therapy to address cognitive comorbidities and disease progression in these patients.

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Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

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Program #/Poster #: 467.17/C40

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National Natural Science Foundation of China (61722313)
National Natural Science Foundation of China (61420106001)
National Key Research and Development Program (2018YFB1305101)

Title: Fmri functional connectivity predicts brain regions of interictal epileptic discharges

Authors: *J. SU[1,2], H. KHOO[3], N. V. ELLENRIEDER[1], L.-L. ZENG[2], D. HU[2], F. DUBEAU[1], J. GOTMAN[1];
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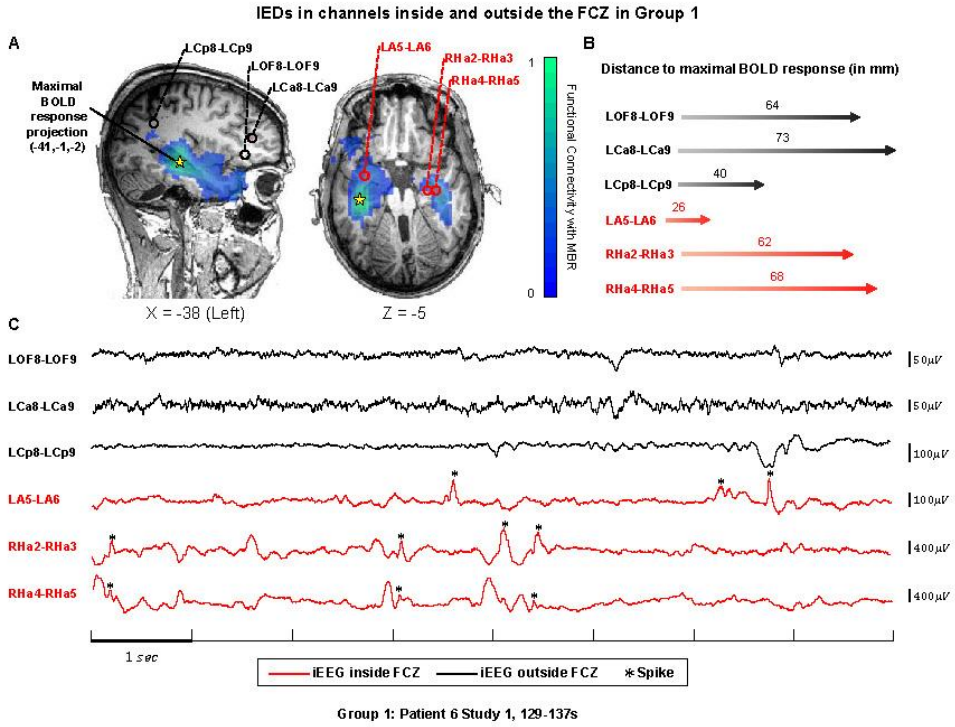
Abstract: Objective: We aim to examine whether regions of Interictal epileptic discharges (IEDs) in intracerebral EEG (iEEG) can be predicted non-invasively by fMRI functional connectivity (FC).
Methods: We studied 38 focal epilepsy patients who underwent simultaneous EEG/fMRI scanning and subsequent intracerebral stereo-EEG investigation. Their scalp IEDs were labelled. In EEG/fMRI analysis, different spatial distributions of IEDs were considered independent studies and IED-related maximal BOLD responses were evaluated using generalized linear model. Studies in which there were iEEG electrodes inside the maximal responses were selected and divided into three groups: Studies with 1. distinct maximal BOLD with t-value clearly higher than other clusters and concordant with seizure-onset-zone (SOZ); 2. Moderate maximal BOLD concordant with SOZ; 3. maximal BOLD discordant with SOZ. Using maximal BOLD as seed, the functionally connected zone (FCZ) was determined. We then use automatic IED detection to label IEDs in iEEG data. IED rates in iEEG channels inside and outside the FCZ were compared in the three groups. The effect of laterality (whether channels are in the same hemisphere as maximal BOLD) and distance between channels and maximal BOLD were considered. Correlation between functional connectivity values and IED rates were also analyzed.
Results: 36 studies in 25 patients were included. IED rates inside the FCZ were higher than outside in Group 1 ($p=2.6\times10^{-6}$) and Group 2 ($p=0.001$) and the inside-outside difference remained after regressing distance and laterality factors (Group 1, $p=1.5\times10^{-6}$; Group 2, $p=0.013$). In Group 1, FC values were correlated with IED rates in channels inside the FCZ ($p<0.05$).
Conclusions: Our results demonstrate a higher probability of finding IEDs in the FCZ of SOZ-concordant maximal BOLD responses than in other regions, regardless of distance and laterality. In studies with distinct maximal BOLD, functional connectivity values can partially predict IED rates. It is thus feasible to non-invasively infer probable brain regions exhibiting IEDs.



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Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

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Program #/Poster #: 467.18/C41

Topic: B.10. Epilepsy

Title: Activation of the instrinsic apoptotic pathway in the cerebellum of kindled rats

Authors: *E. M. TADDEI LIZÁRRAGA[1], C. R. OSORNIO[1], M. RUBIO[2], C. MENDOZA[1], C. TREJO[3], V. CUSTODIO[1], L. HERNANDEZ[1], E. GONZALEZ[1], C. PAZ[1];
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Abstract: The signaling cascades that lead to apoptosis are divided in two main categories: the intrinsic and extrinsic pathways. Experimental studies in epilepsy models have demonstrated the presence of extrinsic apoptotic neuronal death in the cerebellum, with the loss of Purkinje cells. However, the exact mechanism by which apoptosis occurs in the cerebellum has not yet been

elucidated. The intrinsic pathway results in activation of either anti-apoptotic (Bcl-2) or pro-apoptotic proteins (Bid, Bax and cytochrome C), and has been shown to play a role in a number of neurodegenerative diseases. Therefore, we hypothesize that epileptic activity will modify the intrinsic apoptotic pathway as well. We performed Western blot and immunohistochemistry determinations in the cerebellar tissue of rats exposed to amygdaloid kindling. An increase in protein activation of caspases 8 and 9, as well as a decrease in the expression of Bcl-2 was observed. In addition, we found a cytosolic immunopositivity for cytochrome C and mitochondrial immunolocalization of truncated Bid and Bax. Caspase-8 activates the intrinsic pathway releasing Bid, which performs mitochondrial translocation of Bax, inactivating Bcl-2 and allowing the release of cytochrome C through the mitochondrial permeability transition pore, promoting the activation of caspase-9, which in turn activates caspase-3, the main executor caspase of apoptosis. Therefore, we conclude the intrinsic apoptotic pathway is involved in cerebellar neuronal death. These results give us a broader perspective on the mechanisms underlying neuronal loss following epileptic seizures and are an important contribution to the pathophysiology of epilepsy.

Disclosures: E.M. Taddei Lizárraga: None. **C.R. Osornio:** None. **M. Rubio:** None. **C. Mendoza:** None. **C. Trejo:** None. **V. Custodio:** None. **L. Hernandez:** None. **E. Gonzalez:** None. **C. Paz:** None.

Poster

467. Epilepsy: Post-Seizure Mechanisms and Human Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 467.19/C42

Topic: B.10. Epilepsy

Support: American Epilepsy Society Clinical Investigator Training Award

Title: Using Epileptogenicity Index to quantify the characteristics of the epileptic network in a diverse clinical dataset

Authors: *G. SMITH[1], W. C. STACEY[2];
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Abstract: Objective and Rationale
When clinicians analyze intracranial EEG, they rely on both interictal and ictal biomarkers of the location of seizure onset. Quantitative research has revealed several quantitative measures of the behavior of the epileptogenic network. One such measure is the Epileptogenicity Index (EI). In the current study, we applied EI to the EEG of patients in a database of clinical intracranial EEG recordings to test the feasibility of applying this method in a diverse clinical dataset.
Methods

We used clinical data from intracranial EEG recordings from pediatric and adult patients evaluated at our institution. Using the method of calculation of EI previously described, we first calculated a measure of the ratio fast to slow energy spectra at each sample in a snippet of EEG surrounding a seizure. This calculation was performed on up to 5 of each of the types of seizures captured for each patient. Next, the EI was calculated using the Page-Hinckley algorithm to detect the moment when the energy ratio changed to favor high frequency activity at the start of seizure in each channel. Finally, we counted the frequency with which this algorithm produced a robust measure of EI.

Results

This analysis was performed in a total of 61 seizures from 14 different patients taken from a consecutive cohort including all patients who underwent intracranial EEG monitoring at the University of Michigan. Patients were included if clinical data and intractanial EEG data were available at the time of analysis. In 4/14 patients this algorithm did not yield a reliable EI value; in 7/14 patients the algorithm yielded consistently reliable EI values, and in 3/14 patients the algorithm did not yield a reliable EI value in a subset of seizures or seizure types. In 46/61 seizures the algorithm yielded a reliable measurement of EI.

Discussion

These results show that calculation of EI, which depends on a transition from low-frequency to high-frequency spectral power at seizure onset, is a robust measure of epileptogenicity in 75% of the patients tested. This analysis also shows that a subset of seizure onset is characterized by some other pattern. For instance, rhythmic spiking less than 12 Hz at seizure onset causes a decrease in energy ratio, leading to an inability to accurately detect seizure onset with the algorithm. Thus, EI is a robust measure in the majority of seizures detected by intracranial EEG in this cohort; however, some patients have seizures that are not amenable to this method. Further research should be aimed at developing quantitative measures of seizure onset that capture the diversity of seizure onset types.

Disclosures: **G. Smith:** None. **W.C. Stacey:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.01/C43

Topic: B.11. Glial Mechanisms

Support: KAKENHI JP17H02220
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AMED 18dm0107087
The Uehara Memorial Foundation

Title: Upregulation of Fstl1 and Ifitm3 in astrocytes mediate neurodevelopmental impairment induced by innate immune activation

Authors: *T. NAGAI, N. ITOH, S. YAMADA, K. YAMADA;
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Abstract: Immune activation in the CNS is associated with the pathophysiology and/or etiology of psychiatric disorders. Polyriboinosinic-polyribocytidylic acid (polyI:C) triggers a strong innate immune response that mimics immune activation by viral infections. Induction of interferon-induced transmembrane 3 (Ifitm3) in astrocytes has a crucial role in polyI:C-induced neurodevelopmental abnormalities. We previously identified follistatin-like 1 (Fstl1) in polyl:C-induced neurodevelopmental impairment. In the present study, we characterized the Ifitm3-dependent inflammatory processes focusing on astrocyte-derived Fstl1 following polyI:C treatment to assess the neuropathologic role of Fstl1. Astrocytes were treated with PBS (control) or polyI:C. The conditioned medium was collected 24 h after the polyI:C treatment and used as astrocyte condition medium (ACM). The expression of Fstl1 mRNA and extracellular Fstl1 protein levels were analyzed by quantitative PCR and western blotting, respectively. For functional studies, neurons were treated with ACM and the effects of ACM on dendritic elongation were assayed. To examine the role of Fstl1, recombinant Fstl1 protein and siRNA for Fstl1 were used. To investigate the expression of Fstl1 in vivo, neonatal mice were treated with vehicle or polyI:C on postnatal day2 to 6. ACM prepared with polyI:C (polyI:C ACM) contained significantly higher Fstl1 protein than control ACM, but no increase in Fstl1 was observed in polyI:C ACM derived from Ifitm3-deficient astrocytes. We found that the production of Fstl1 involves the inflammatory responsive molecule Ifitm3 in astrocytes and influences neuronal differentiation. The levels of Fstl1 increased in the hippocampus of polyI:C-treated neonatal mice. COS7 cells co-transfected with both Fstl1 and Ifitm3 had higher extracellular levels of Fstl1 than the cells transfected with Fstl1 alone. Treatment of primary cultured hippocampal neurons with recombinant Fstl1 impaired dendritic elongation, and the deleterious effect of polyI:C ACM on dendritic elongation was attenuated by knockdown of Fstl1 in astrocytes. These results suggest that the extracellular level of Fstl1 is regulated by Ifitm3 in astrocytes, which could be involved in polyI:C-induced neurodevelopmental impairment.

Disclosures: T. Nagai: None. **N. Itoh:** None. **S. Yamada:** None. **K. Yamada:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.02/C44

Topic: B.11. Glial Mechanisms

Support: NIH NS092785

NIH NS092466

Title: Astrocyte Panx1 prevents status-induced social behavior deficits

Authors: A. CIBELLI[1], P. OBOT[2], J. VELISKOVA[2], L. VELISEK[2], *E. SCEMES[2];
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Abstract: Early life seizures can lead to cognitive and behavioral deficits with several reports indicating a strong association between epilepsy and autism spectrum disorder (ASD). Pannexin 1 (Panx1) is an ATP release channel present in astrocytes as well as in neurons with strong relation to seizures. Our previous work showed that, in juvenile mice, Panx1 promotes status epilepticus (SE) induced by kainic acid (KA). More recently, by using conditional knockout mice, we showed that astrocyte but not neuronal Panx1 has protective effects in the KA model, delaying the onset of SE and improving seizure outcome. To determine the extent to which astrocyte Panx1 protects against behavioural impairments resultant from KA-induced seizures, we evaluated the mice 5 weeks following KA-induced seizures for possible sociability deficits (a hallmark of ASD). Three weeks old male and female Panx1$^{f/f}$, GFAP-Cre:Panx1$^{f/f}$, NFH-Cre:Panx1$^{f/f}$, and Panx1-null mice were i.p. injected with KA (20mg/kg). Mice that developed SE for at least 60 min were then evaluated for sociability 5 weeks later. We used the automated three-chambered apparatus to assess social interaction of KA-exposed and age-matched naive mice. The software (Any-Maze) quantifies direct social approach behavior when a subject mouse is presented with the choice of spending time with either a stranger mouse (A) or an object (O). Sociability was defined as the subject mouse spending more time in contact with *A* than with *O*. Repeated measures one-way-ANOVA was used for statistical analysis and significance set at $P< 0.05$. Six to 8 mice per group were used. The mice of all genotypes not exposed to seizures spent more time with the stranger mouse (~ 145 sec) than with the object (~45 sec). Five weeks after KA-induced seizures, Panx1$^{f/f}$ and GFAP-Cre:Panx1$^{f/f}$ mice displayed social deficits, spending comparable time with *A* (~ 70 sec) and *O* (~50 sec), while the NFH-Cre:Panx1$^{f/f}$ and Panx1-null mice did not show the social deficits, spending more time (~140 sec) with *A* than with *O* (~60 sec). Thus, the global deletion of Panx1 or the presence of Panx1 in astrocytes have protective effects on seizure-induced social behaviour deficits. These results not only indicate that Panx1 might be a potential therapeutic target to treat seizures and associated social deficits, but also highlight the importance that astrocyte Panx1 plays in preventing seizure-induced behavioural sequels.

Disclosures: **A. Cibelli:** None. **P. Obot:** None. **J. Veliskova:** None. **L. Velisek:** None. **E. Scemes:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.03/C45

Topic: B.11. Glial Mechanisms

Support: The Glaucoma Foundation (SK)
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National Eye Institute, #EY015672 (PK)
Illinois Society for the Prevention of Blindness (AKG)

Title: Glioprotection by a synthetic metalloporphyrin superoxide dismutase mimetic

Authors: *A. K. GHOSH[1,2,3,4,5], V. R. RAO[3,4], P. KOULEN[6], E. B. STUBBS, Jr.[3,4], S. KAJA[1,2,3,4];
[1]Grad. Program in Neurosci., [2]Mol. Pharmacol. and Therapeut., [3]Ophthalmology, Loyola Univ. Chicago, Maywood, IL; [4]Res. Service, Edward Hines Jr. VA Hosp., Hines, IL; [5]Discovery Res., eyeNOS Inc., Oak Park, IL; [6]Vision Res. Center, Departments of Ophthalmology and Biomed. Sci., Univ. of Missouri - Kansas City Sch. of Med., Kansas City, MO

Abstract: Clinical evidence suggests a pathological role of increased levels of oxidative stress in many neurodegenerative diseases, including glaucoma. In all subtypes of glaucoma, optic nerve head astrocytes (ONHAs) undergo reactive astrocytosis, which is the mechanism underlying the clinically observed optic nerve head remodeling. Metalloporphyrin superoxide dismutase (SOD) mimetics are potent antioxidants with a well-documented safety profile. The purpose of this study was to determine whether the metalloporphyrin SOD mimetic, manganese(III) tetrakis(1-methyl-4-pyridyl) porphyrin (Mn-TM-2-PyP), exerts glioprotective effects against reactive astrocytosis-induced sensitization to oxidative stress. We have previously shown that reactive astrocytosis results in a significant increase in celluar oxidative stress levels, as quantified using dichlorofluorescein and CellROX®fluorescence. Primary adult rat optic nerve head astrocytes (ONHAs) were pre-treated for one hour with 0.005% Mn-TM-2-PyP or vehicle. ONHAs were then exposed to ambient or hyperbaric pressure (25 mmHg above ambient) to induce reactive astrocytosis and subsequently to chemically-induced oxidative stress using *tert*-butyl hydroperoxide (tBHP; 0 to 1 mM). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) uptake and lactate dehydrogenase (LDH) release assays for cell viability and proliferation were performed to determine glioprotective potential. Reactive astrocytosis shifted both the $IC_{50}$for tBHP in the MTT assay and the EC_{50} for tBHP in the LDH assay by > 80 μM.

Mn-TM-2-PyP fully prevented loss of cell viability in response to oxidative stress. Furthermore, Mn-TM-2-PyP resulted in a 2-fold increase in nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein levels ($P<0.05$), the transcriptional regulator of the antioxidant response element (ARE), and an 8-fold upregulation of mitochondrial SOD2 ($P<0.001$). No change was observed in NADPH oxidase 4 (NOX4) expression. Our data suggest that reactive astrocytosis in ONHAs results in elevated levels of oxidative stress that can be fully prevented by a manganese porphyrin antioxidant. The glioprotective potential of Mn-TM-2-PyP was attributed to its SOD mimetic activity and its ability to induce upregulation of endogenous antioxidant enzymes. Our data support the continued preclinical development of antioxidant approaches for glaucoma.

Disclosures: **A.K. Ghosh:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); K&P Scientific LLC, EyeNOS Inc., Experimentica Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); EyeNOS Inc.. F. Consulting Fees (e.g., advisory boards); K&P Scientific LLC. **V.R. Rao:** None. **P. Koulen:** None. **E.B. Stubbs:** None. **S. Kaja:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Experimentica Ltd., K&P Scientific LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Experimentica Ltd., K&P Scientific LLC.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.04/C46

Topic: B.11. Glial Mechanisms

Title: Astrocyte dynamics at different stages of cuprizone treatment

Authors: *L. G. FRANKLE, J. SHELESTAK, R. CLEMENTS;
Kent State Univ., Kent, OH

Abstract: Cuprizone is a copper chelator that demyelinates neurons and is used to model demyelinating and degenerative diseases. Our previous work using glial fibrillary acidic protein (GFAP) staining confirmed a pattern of activation including increased process number and branching after three, four, and six weeks of cuprizone treatment. The current phase of the project probes whether similar patterns are observed at one or two weeks of cuprizone treatment as well as when such changes begin and what astrocyte subtypes become prevalent at these early stages. Animals were fed 0.2% cuprizone chow ad libitum for one or two weeks, sacrificed, dissected, and their brains halved with one half stained using GFAP and DAPI and imaged using confocal microscopy with astrocytes in the corpus callosum assessed for activation, and one half processed through Western blot. Western blots measured levels of tumor necrosis factor alpha

(TNF-α), interferon gamma (IFN-**γ**), complement component 3 (C3), and epithelial membrane protein 1 (Emp1), in the whole-cell lysate of homogenized samples taken from the corpus callosum or cortex of control and experimental animals. C3 is known to be upregulated in astrocytes that have an A1 reactive phenotype, which releases cytokines that inhibit axonal regrowth and cause death of neurons and oligodendrocytes, as well as by other cell types such as mast cells and macrophages in times of stress. TNF-α along with IL-1α and complement component 1 q (C1q), cause A1 reactivity, as well as contributing to gliosis and demyelination. IFN-**γ** is produced by T cells and natural killer cells of the immune system, but it is also produced by reactive astrocytes, macrophages and microglia. It acts on astrocytes and other glial cells to promote gliosis and inhibit remyelination, both of which are relevant to measuring the progression of cuprizone toxicity. Emp1 is upregulated in another type of activated glial phenotype that is less detrimental - A2. This type is associated with ischemic models and promotes synaptogenesis as well as neuronal and oligodendrocyte survival and outgrowth. Relative levels of A1 and A2 activation are relevant to the progression of the cuprizone toxicity since A1 astrocytes contribute to demyelination and neural disruption and A2 astrocytes preserve neural and oligodendrocyte maintenance. To confirm that presence assessed by Western blot represented astrocyte protein levels of C3 and Emp1, immunofluorescence was employed on fixed tissue slices taken at one and two weeks of cuprizone treatment. Levels of A1 and A2 astrocytes reveal the glial response to cuprizone toxicity and may help elucidate the role of astrocyte pathology in demyelinating states.

Disclosures: L.G. Frankle: None. **J. Shelestak:** None. **R. Clements:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.05/C47

Topic: B.11. Glial Mechanisms

Support: NIH-RO1-NS036692
NIH-RO1-NS082851
NIH-RO1-NS052634

Title: Glia-perineuronal net interaction in physiology and pathophysiology

Authors: *B. P. TEWARI[1], K. J. ENGEL[3], L. CHAUNSALI[2], A. WOO[3], I. KIMBROUGH[3], D. C. PATEL[1], H. SONTHEIMER[4];
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Abstract: Extracellular matrix (ECM) in the central nervous system (CNS) forms highly organized lattice like structures called perineuronal nets (PNNs), which encapsulate fast spiking interneurons (FSNs) in the cerebral cortex and CA2 pyramidal neurons in the hippocampus. PNN lattice is composed of chondroitin sulfate proteoglycans (CSPGs), Hyaluronic acid (HA), tenascin R, etc. and lattice holes confine the axosomatic synapses. PNN forming ECM proteins and proteoglycans are secreted by astrocytes, which also perform homeostatic functions including glutamate clearance and extracellular potassium buffering. Previously, we have shown that PNNs modulate biophysical properties of the enclosed interneurons and are prone to degradation by matrix remodeling enzymes such as matrix metalloproteinases (MMPs) released in glioma-associated epilepsy. In the present study, we hypothesized that PNN lattice constitutes a spatial proximity barrier, due to which PNN holes define the placement sites for astroglial processes and axosomatic synaptic contacts, i.e. the tripartite synapse. Consequently, the PNN holes act as units of astroglial homeostatic functions and axosomatic synaptic activity. Our data suggest that astroglial processes are confined to the PNN holes and constitute a non-overlapping spatial interface with PNN CSPGs in both cerebral cortex and hippocampus. PNN expressing neurons possess significantly smaller astroglial coverage area than the PNN lacking neurons suggesting an inhibitory role of PNNs for astroglial spatial proximity to the FSNs. Moreover, in the PNN holes, presence of astroglial processes expressing homeostatic proteins including Kir4.1 and Glt1, in addition to the excitatory and inhibitory presynaptic and postsynaptic terminals, suggest them analogous to the tripartite synapses. We also observed disruption of astrocyte-PNN spatial interface upon experimental PNN degradation in mouse brain *in-vivo* using Chondroitinase ABC enzyme and in a mouse model of glioma-associated epilepsy. Our data suggest that degradation of ECM and PNN assembly under various CNS pathologies characterized by elevated release of matrix remodeling enzymes, may similarly alters the astroglial-PNN spatial interface thereby rendering the units of astroglial homeostatic functions and axosomatic synaptic activity dysfunctional.

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Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.06/C48

Topic: B.11. Glial Mechanisms

Title: Astrocyte influence on GABA catabolism in an iPS cell model system

Authors: *T. E. R. SCHNEIDER[1], S. ROSAS[1], J. V. MCGIVERN[2];
[2]Biochem., [1]Lakeland Univ., Plymouth, WI

Abstract: Succinic semialdehyde dehydrogenase deficiency (SSADHD) is a rare autosomal recessive disorder that presents itself in early childhood through a wide range of severities from patient to patient. The molecular cause of the disorder is due to a mutation in the metabolic enzyme, succinic semialdehyde dehydrogenase (SSADH), which is essential for the proper catabolism of the neurotransmitter γ-aminobutyric acid (GABA). In the cerebrospinal fluid of patients with SSADHD there is a 2-4 fold increase in GABA levels and nearly 30 fold increase in gama-hydroxybutyrate (GHB). Most models have focused on the neuronal aspects of the disease, but our focus using induced pluripotent stem cells has been to examine the glial contribution. We have discovered, using a low cost neurosphere method, that our GFAP+ astrocytes possess the glial transporter GAT3 after a six week differentiation process. This suggests glial cells in our cultures do in fact have the capacity to take up GABA from the media. In order to directly assess the ability for glial tissue to regulate GABA levels in our media conditions we have been exploring both HPLC and ELISA methods to quantify GABA levels. Finally, in order to fully utilize this system to study SSADHD, we are generating an SSADH knockout using CRISPR/Cas9. Establishing glial culture conditions that can be monitored for neurotransmitter catabolism may be a powerful tool for studying the influence of glia not only for SSADHD but for a wide range of neurological diseases.

Disclosures: T.E.R. Schneider: None. **S. Rosas:** None. **J.V. McGivern:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.07/C49

Topic: B.11. Glial Mechanisms

Support: National Institute of Mental Health

Title: Investigating the role of glia astrocytes in Parkinson's disease by using a computational model of astrocytes

Authors: *Z. SAJEDINIA[1], S. HELIE[2];
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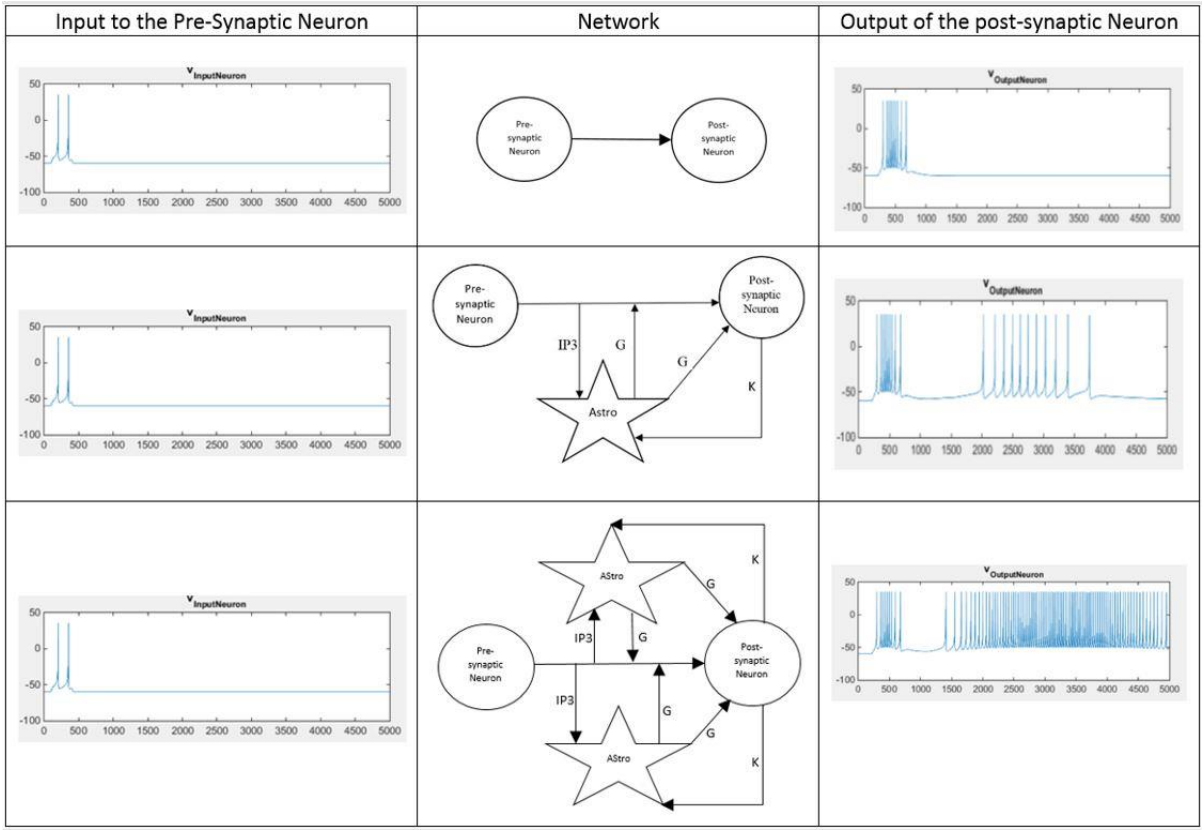
Abstract: Recent findings show that astrocytes are involved in initiation and progression of neurodegenerative diseases. Some studies show that the number of astrocytes increases in Parkinson’s disease (PD), and because astrocytes interfere with neural signaling, we expect to observe abnormal firing patterns in PD-related neural networks. While some studies show an abnormal increase in firing rate (neural bursting) in PD, it has not been shown whether this abnormality relates to the PD excess astrocytes. To investigate this relationship, we need to be able to study astrocytes independently. However, because neurons and astrocytes share many of

the same neurotransmitter receptors, performing physiological experiments on astrocytes is difficult. To overcome this difficulty, computational models could be helpful and an appropriate choice. First, we need a computational model of astrocytes. However, unlike neurons, computational models of glia cells have not yet received much attention. To date, a few computational models of astrocytes have been proposed but none of them is fully functional and widely accepted. In this work, we present a computational model of astrocytes based on the Izhikevich simple model of neurons. First, we include this astrocyte model in one synapse. We show that increasing the number of astrocytes in this synapse results in an increase in neural firing rate (as we see in PD). Second, we extend the model and make a neuron-astrocyte spiking network. Similarly, by increasing the number of astrocytes we show the impairment of the network in categorizing different stimuli. These results suggest the potential involvement of astrocytes in PD, who show a similar deficit in category learning. Because previous computational models of PD have focused only on neurons and did not consider the changes in neural signaling caused by astrocytes, we argue that a more accurate model of PD should include a model of astrocytes in related underlying networks. We hope that this line of research will help understand the underlying mechanisms in PD and suggest new astrocyte targeted treatments for PD.



Disclosures: **Z. Sajedinia:** None. **S. Helie:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.08/C50

Topic: B.11. Glial Mechanisms

Title: Fibrinogen chains intrinsic to the brain

Authors: *E. V. GOLANOV[1], M. A. SHARPE[1], A. S. REGNIER-GOLANOV[1], G. J. DEL ZOPPO[2], D. S. BASKIN[1], G. W. BRITZ[1];
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Abstract: Fibrin deposition along paravascular spaces can be observed in naive animals and increases following subarachnoid hemorrhage (SAH) involving areas remote from the hemorrhage. Astrocyte (Astro) endfeet form the *glia limitans* (GL) and sheath of intracerebral vessels and express the procoagulant tissue factor (TF). It has been assumed that fibrinogen enters the subarachnoid space through damaged microvessel blood-brain barrier or ruptured vessels. Based on our observation we hypothesize that fibrinogen chains (FC) Aα, Bβ and γ are synthesized by astrocytes. Here we demonstrate *in vivo* and *in vitro* that astroglia are capable of FC expression. SAH in mice was induced by Circle of Willis perforation (control was without perforation). Four days later, mice were anesthetized, perfused, and fixed. Whole brains were processed for immunohistochemical (IHC) analysis of the presence of fibrin or FC on the brain surface. Coronal slices were processed for detection of FC Aα, Bβ, γ and GFAP and IHC was quantitively analyzed. Human brain slices were processed for detection of FC using DAB. For *in vitro* analysis normal human Astro (NHA) were grown to confluence and stimulated with the nitric oxide donor NOC-18 (100 μM), TNF-α (100 nM), and the stable ATP analogue ATP-γ-S (100 μM) for 4 hours. Cultures were fixed, washed/permeabilized, and processed for quantitative immunofluorescence (IF). Four days after SAH FC Aα IF associated with GL increased 3.2 and 2.5 times ($p<0.05$ and $p<0.01$) on the ventral and dorsal brain surfaces, respectively; FC Bβ increased by 3 times ($p<0.01$) on the dorsal surface, and FC γ increased by 3 times ($p<0.01$) on the ventral surface compared to sham animals. FC IF in astrocytes was also observed in the brain parenchyma. NHA constitutively expressed all three FCs. Application of specific siRNA suppressed FC Aα by 76% ($p=0.038$), Bβ by 80% ($p=0.018$) and γ by 78% ($p=0.025$). The FC expression by cultured NHA was differentially affected by biologically significant stimuli. Analysis of human brain tissue samples obtained from different brain sites revealed FC immunoreactivity in astrocytes, suggesting that human brain cells also are capable of expressing FC. We demonstrated for the first time presence that astrocytes are capable of FC expression, which differentially responded to biologically significant stimuli. SAH is followed by increased expression of FCs associated with GL remote from the hemorrhage as well as in brain

parenchyma. There is a possibility that individual FCs can play multiple physiological roles. We conclude that astrocytes are capable of production of FCs, which may be involved in various normal and pathological brain processes.

Disclosures: E.V. Golanov: None. **M.A. Sharpe:** None. **A.S. Regnier-Golanov:** None. **G.J. Del Zoppo:** None. **D.S. Baskin:** None. **G.W. Britz:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.09/C51

Topic: B.11. Glial Mechanisms

Support: Hillman Foundation GRANT109033

Title: Telencephalic astrocytes display no regional heterogeneities in stress responses and do not forfeit their neuroprotective roles after surviving intense oxidative stress

Authors: *T. N. BHATIA, D. B. PANT, J. N. WEILNAU, E. A. ECKHOFF, R. N. GONGAWARE, T. DO, D. F. HUTCHISON, A. M. GLEIXNER, R. K. LEAK;
Div. of Pharmaceut. Sci., Duquesne Univ., Pittsburgh, PA

Abstract: Astrocytes have evolved to protect neurons, but it is not known whether they lose some of their neuroprotective abilities under conditions of severe oxidative toxicity. In the present study, we report that primary cortical astrocytes surviving severe paraquat toxicity display stress-reactivity, but continue to tolerate a second toxic paraquat hit of the same intensity, without any additional cell loss. Inhibition of multiple stress-responsive molecules (heat shock protein 70, heme oxygenase-1, glutathione, ERK1/2, Akt, and JNK), either alone or in combination, did not abolish or even attenuate astrocytic stress tolerance. Primary cortical astrocytes surviving these high concentrations of paraquat exhibited Nrf2 activation and higher glutathione content. In primary neuron/astrocyte bilayer cultures, astrocytes surviving intense oxidative toxicity continued to protect neighboring neurons from paraquat exposure, even at high paraquat concentrations that killed 80% of neurons in control monolayer neuron cultures. These findings suggest that stress-reactivity does not inescapably lead to the acquisition of neurotoxic phenotypes in astrocytes. Next, we tested whether astrocytes collected from different subregions of the telencephalon would differ in their capacities to survive intense oxidative and proteotoxic stressors. Unexpectedly, full concentration-response curves revealed that primary astrocytes harvested from the neocortex, entorhinal/piriform allocortex, and hippocampal allocortex were all equally vulnerable to paraquat and proteasome inhibitors (MG132 and lactacystin), and, further, displayed equivalent degrees of stress tolerance against dual hits. All three types of astrocytes also responded similarly to loss of Hsp70 or glutathione synthesis when exposed to

proteotoxic stress. In contrast to astroglia, primary neurons harvested from the same telencephalic subregions clearly displayed selective vulnerabilities to oxidative and proteotoxic stressors. These data support heterogeneity in stress responses in neurons, but not in astrocytes of the telencephalic edifice, and suggest that therapies designed to inhibit these natural stress responses may hasten, rather than lessen neurodegeneration.

Disclosures: T.N. Bhatia: None. **D.B. Pant:** None. **J.N. Weilnau:** None. **E.A. Eckhoff:** None. **R.N. Gongaware:** None. **T. Do:** None. **D.F. Hutchison:** None. **A.M. Gleixner:** None. **R.K. Leak:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.10/C52

Topic: B.11. Glial Mechanisms

Support: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
NIH F32-087783
LLHF

Title: Reactive astrocyte heterogeneity after stroke: Identifying region-specific targets for neural repair

Authors: *A. J. GLEICHMAN, R. KAWAGUCHI, M. V. SOFRONIEW, G. COPPOLA, S. CARMICHAEL;
UCLA Sch. Med., Los Angeles, CA

Abstract: Stroke is one of the most common forms of death and disability worldwide, yet few treatment options exist. Tissue repair and recovery after injury is a complex process, involving both scar formation around the site of the injury that likely isolates the damage and prevents spread of immune-related damage molecules as well as remodeling of the neighboring and, in some cases, contralateral tissue. Astrocytes are central to these processes and respond differently in these distinct compartments. While it has long been clear that astrocytes respond to damage in a gradated fashion, the details of these responses are unknown. Here, we use morphologic and phenotypic tools to identify distinct zones of reactive astrocytes after stroke, which we used to inform a transcriptomic analysis to comprehensively map zone-specific astrocytic responses to both white matter and cortical stroke. We are using these transcriptomic maps to identify potential intervention points to promote repair and recovery, with a particular focus on astrocytic control of vascular development after white matter stroke. In order to map the morphologic changes astrocytes undergo after stroke, we developed astrocyte-specific spaghetti monster reporter lentiviruses, injected them sparsely into the cortex or white matter at the time of stroke,

and assessed individual astrocyte morphology at 7 days post-stroke. We also assessed phenotypic changes in post-stroke astrocytes, using markers for proliferation, reactivity, and proteins previously identified as differentially regulated by stroke. Astrocytes undergo stereotyped morphologic and phenotypic changes in both stroke models based on the distance from the infarct border. These differences were used to define zones of reactivity that were then analyzed transcriptomically. To map the transcriptomic changes zone-specific astrocytes undergo after stroke, we used GFAP-Cre/Ribotag mice to selectively isolate astrocyte-enriched mRNA in laser captured reactive astrocyte zones. While some transcriptomic changes are preserved between white matter and cortical stroke, others are not, with potential functional consequences for the recovering tissue. In particular, cortical astrocytes appear to trigger greater angiogenesis and vessel maturation after stroke than do white matter astrocytes. Angiogenesis has been associated with increased recovery after gray matter stroke; using the transcriptomic analyses of gray matter stroke, we are investigating the repair potential of astrocyte-induced angiogenesis in white matter stroke.

Disclosures: A.J. Gleichman: None. **R. Kawaguchi:** None. **M.V. Sofroniew:** None. **G. Coppola:** None. **S. Carmichael:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.11/C53

Topic: B.11. Glial Mechanisms

Support: MOST 106-2320-B-010 -008 -MY3 from Ministry of Science and Technology, Taiwan

Title: Roles of neural aryl hydrocarbon receptor in glutamate homeostasis and neuropsychiatric disturbance in chronic kidney disease mouse model

Authors: *Y.-J. HUANG[1], C.-J. LU[2], H.-C. LIN[1,3], P.-C. HSU[1], D.-C. TARNG[1,4,5], Y.-H. LEE[1,3];
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Abstract: Chronic kidney disease (CKD) is a progressive loss of renal function that gives rise to accumulation of uremic toxins such as blood urea nitrogen and indoxyl-3-sulfate (I3S) in the blood that causes multiple organ pathology. I3S is a potent physiological agonist of aryl hydrocarbon receptor (AhR), a ligand-activate transcription factor that can be activated by

environmental hormones and endogenous tryptophan metabolites. Notably, I3S toxicity is attributed to its protein-bound property that cannot be removed by hemodialysis, and can penetrate blood brain barrier. Recent studies indicated mental disturbance and cognitive impairment in CKD patients, but the involvement of brain AhR was unknown. In this study, we investigated the molecular mechanism of AhR-mediated glutamate transporter (GLT1) alteration and the subsequent impact on cognitive function in CKD. First, we establish the I3S chronic treatment in cultured astrocytes to mimic the accumulation of I3S *in vivo*. The data showed that I3S can activate AhR and produce reactive oxygen species (ROS). Heme oxygenase-1 (HO-1), an antioxidant protein, was elevated and further increased by AhR antagonist CH223191 treatment in both acute and chronic I3S incubation in cultured astrocytes. Besides, chronic I3S exposure led to GFAP activation and GLT1 reduction, accompanied with the impairment of glutamate uptake activity, and these effects can be reversed by CH-223191. Notably, AhR inhibition could increase surface GLT1 protein expression in cultured astrocytes. We established a 5/6 nephrectomy CKD mouse model that has elevated I3S concentration in both plasma. The data showed that CKD decreased GLT1 and increased reactivated astrocytes in the anterior cortex, with the effect attenuated in the neural lineage-specific nestin-Cre/AhR-floxed (nAhRCKO) mice. Furthermore, nAhRCKO CKD mice showed less anxiety-like behavior and better recognition memory than wild type CKD mice. Thus, chronic I3S accumulation in the brain may cause astrocytic GLT1 hypofunction to disturb glutamate homeostasis in an AhR-dependent manner, which may contribute to the mood disturbance and cognitive declination in CKD.

Disclosures: **Y. Huang:** None. **C. Lu:** None. **H. Lin:** None. **P. Hsu:** None. **D. Tarng:** None. **Y. Lee:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.12/C54

Topic: B.11. Glial Mechanisms

Support: NIRG-12-241456
1K01AG042500
NIH-NIGMS 5P20GM103446
NIH-NIGMS 5P20GM103653

Title: Sex differentiated connectivity, behavior (memory and anxiety), and pathology associated with astrocyte specific expression of cytoplasmic TDP-43

Authors: *C. M. KHALID-JANNEY[1], D. CARTER[1], C. SULLIVAN[2], T. WHITE[1], K. WILSON[1], I. SERRANO[1], L. GUZMAN[1], M. CAREY[1], S. A. DAVIS[1], M. A. GITCHO[1]; [1]Biol. Sci., Delaware State Univ., Dover, DE; [2]St. Michael's Col., Colchester, VT

Abstract: TAR DNA binding protein 43 (TDP-43) functions as a heterogeneous nuclear ribonucleoprotein that regulates gene expression, RNA stability, RNA transport and localizes to the cytoplasm as a stress response protein. Glial Fibrillary Acidic Protein (GFAP) is an intermediate filament protein found primarily in astrocytes that increases expression when astrocytes are activated. TDP-43 predominantly resides in the nucleus, except under pathological conditions it aggregates in the cytoplasm. To investigate pathological outcomes and non-cell autonomous effects of this pathological condition in astroglial cells, TDP-43 with a defective nuclear localization signal (ΔNLS) under control of the human GFAP promoter (GFAP-tTA) was selectively and conditionally expressed in astrocytes utilizing a doxycycline inducible system. We hypothesize that selective TDP-43ΔNLS expression in astrocytes alters memory and anxiety through a mechanism of non-cell autonomous neuronal degeneration.

Both GFAP-tTA (control) and GFAP-tTA/TDP-43ΔNLS mice were examined across two time points (8 & 16 weeks) under developmental conditional expression (-DOX) and selective expression post weaning (+DOX). A battery of behavioral tests consisting of anxiety tests (Light/Dark Box, Open Field, Hole Board, Elevated Plus Maze), memory tests (8-Armed Radial Maze (ARM), Y-Maze), and a sociability test (Three Chamber Novel Sociability), in differing combinations at each time point. Pathology and biochemistry in the brain were also evaluated at 8- and 16-weeks. Additionally, primary cortical mouse neuron/astrocyte (~90%/~10%) cultures comparing GFAP-tTA and GFAP-tTA/TDP-43ΔNLS were examined for viability, immunofluorescence, Western blot, and proteomics. Primary cortical neuron/astrocyte co-cultures expressing GFAP-tTA/TDP-43ΔNLS showed a significant decrease in neuronal viability compared with littermate controls.

At 8- & 16-weeks of age, GFAP-tTA/TDP-43ΔNLS mice (-DOX) displayed behavioral changes in anxiety and memory, which may be associated with the changes in non-cell autonomous neuronal degeneration. Similarly, TDP-43ΔNLS (+DOX) mice also showed a gene effect of increased anxiety behaviors as early as ~8-weeks of age. Functional Magnetic Resonance Imaging (fMRI) and structural staining (H&E) staining revealed nuclear condensation and neuronal loss in the hippocampus, specifically in the dentate gyrus.

Identifying and exploring this relationship of non-cell autonomous degeneration may expand our knowledge of astrocyte dysfunction associated with neurodegeneration, as well as also providing insight to associated behaviors of interst.

Disclosures: C.M. Khalid-Janney: None. **M.A. Gitcho:** None. **D. Carter:** None. **T. White:** None. **K. Wilson:** None. **I. Serrano:** None. **L. Guzman:** None. **M. Carey:** None. **S.A. Davis:** None. **C. Sullivan:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.13/C55

Topic: B.11. Glial Mechanisms

Support: GU MCGSO SRGP
NIH T32NS041218
NIH R01NS083410

Title: Organochlorines and brain homeostasis: Polychlorinated biphenyls as astrocytic stressors

Authors: *M. S. MCCANN[1], H. R. FERNANDEZ[1], S. FLOWERS[2], K. A. MAGUIRE-ZEISS[3]; [2]Dept. of Neurosci., [3]Neurosci., [1]Georgetown Univ. Med. Ctr., Washington, DC

Abstract: While the etiology of many neurodegenerative diseases remains elusive, evidence suggests that the intersection of environmental stressors and genetic predispositions result in neurodegeneration. The accumulation of polychlorinated biphenyls (PCBs), a class of hazardous organic chlorines once widely used for industrial purposes, is correlated with increased nigral cell death in Parkinson's disease (PD) patients. Here, we studied the impact of Aroclor 1254, a commercially available and once widely-used PCB mixture, on astrocytes. Astrocytes have a critical role in maintaining homeostasis throughout the brain, including at the synapse and at the blood-brain barrier, and serve as the predominant defense against xenobiotic attack in the central nervous system. We hypothesize that PCBs cause astrocytic oxidative stress and related dysfunction including metabolic disturbances, lipid peroxidation, protein modifications that perturb the ability of astrocytes to perform antioxidant capacity. We treated primary murine cortical astrocytes with PCBs and report an increased antioxidant response (*GSTA2, HMOX1, NOX1)* with concomitant lipid peroxidation (via BODIPY 581/591 oxidation) and protein modifications, as well as mitochondrial respiratory impairments. Together, these data suggest that this persistent environmental toxicant disrupts astrocytic redox which in turn may impair neuronal function and cerebral homeostasis.

Disclosures: M.S. McCann: None. **H.R. Fernandez:** None. **S. Flowers:** None. **K.A. Maguire-Zeiss:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.14/C56

Topic: B.11. Glial Mechanisms

Support: NIH R01
NIH Merit award
Pennsylvania State CURE funding

Title: Investigation of the effect of varying cocaine dosage and RPEC transplantation on astroglial proliferation in cocaine self-administering rats

Authors: *A. KIM, M. P. SUBRAMANIAN, K. VENKITESWARAN, P. S. GRIGSON, T. SUBRAMANIAN;
Pennsylvania State Col. of Med., Hershey, PA

Abstract: It is important to understand the pathogenesis by which cocaine addiction arises, as well as the neurodegenerative effects cocaine has on the central nervous system by way of astrocytosis. Astrocytosis can exacerbate excess inflammatory processes and impair proper axonal regeneration, worsening the neurodegeneration and addiction pathways in the cocaine-affected brain. This cocaine-induced response occurs in the ventral tegmental area (VTA) projecting to the nucleus accumbens (NAc) where amplified astrocytic proliferation may also be seen. This could suggest generalized astrogliosis due to injury or a more specific response leading to a refinement of synaptic connectivity between VTA and NAc neurons. Ultimately, it is important to elucidate the effects cocaine, transplantation and hRPEC introduction into NAc may have on astroglial response in order to better understand the CNS impairment mechanisms of cocaine in the mesolimbic pathway via astroglial influence and how to treat these alterations for victims of cocaine addiction. We assessed the effects of bilateral transplantation of intra-NAc grafts containing growth factor secreting embryonic human retinal pigment epithelial cells (hRPEC) on astroglial proliferation in the VTA of rats trained to self-administer cocaine. Rats were categorized as low or high drug-takers based on the number of cocaine infusion attempts. Separate cohorts were made with rats being treated with either collagen beads (vehicle) or beads attached with hRPECs (20K cells/hemisphere) bilaterally into the medial shell of the NAc. Additionally, rats that self-administered cocaine for 2 days without any surgical intervention were utilized as controls. All rat brain sections were stained for glial fibrillary acidic protein (GFAP), using rabbit polyclonal anti-GFAP antibody. For quantitating astroglial response, stereology using systematic random sampling was used to discern significant differences among groups. Gross histology and preliminary astrocyte counts demonstrate a notable decrease in astrogliosis from the day 2-control rat sections vs. the hRPEC-treated cohort. This comparison

held true between these groups in the high and low-drug takers. There was also a decrease in the astroglial counts from the vehicle-treated rats to that of the hRPEC-treated cohort. Further workup will be done to confirm these results, as more rat brains need to be analyzed to increase sample size, and ANOVA statistical analysis will be applied to assess for statistical significance of these observations. Should our hypothesis hold true, hRPEC would mitigate astrogliosis in the VTA of cocaine-addicted rats and enhance neuronal survival.

Disclosures: A. Kim: None. **M.P. Subramanian:** None. **K. Venkiteswaran:** None. **P.S. Grigson:** None. **T. Subramanian:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH R01, Penn State College of Medicine. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Adamas, Teva, Acadia, US World Meds. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Tyler Francis Publishing, Adamas, Teva, Acadia, US World Meds.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.15/C57

Topic: B.11. Glial Mechanisms

Support: NIH Grant R01AA021468
NIH Grant R01AA022948
VA Merit Review Award I01BX001819

Title: Effect of third-trimester of human gestation-equivalent ethanol exposure on hippocampal astrocyte extracellular matrix and DNA methyl transferases gene expression *in vivo*

Authors: *M. GUIZZETTI, J. G. HASHIMOTO, K. R. MCNEALY;
Oregon Hlth. and Sci. Univ. & Portland VA, Portland, OR

Abstract: Prenatal ethanol exposure can cause Fetal Alcohol Spectrum Disorders (FASD), characterized by cognitive and behavioral dysfunctions and increased incidence of psychiatric disorders later in life. We have reported that ethanol exposure in astrocytes changes the levels of several extracellular matrix (ECM) proteins and proteases resulting in altered neuronal development *in vitro*. We have also reported that neonatal (equivalent to the third-trimester of human gestation) ethanol exposure in rats alters hippocampal neuron morphology and the expression of ECM-related genes and proteins *in vivo*. In the present study we have examined the effects of ethanol on gene expression of ECM related proteins and DNA methyltransferases

(*Dnmt*) selectively in hippocampal astrocytes using the translating ribosome affinity purification (TRAP) procedure with transgenic Aldh1l1-EGFP-Rpl10a mice that expresses ribosomal protein Rpl10a tagged with eGFP in cells expressing the astrocytic marker *Aldh1l1*.Litters of Aldh1l1-EGFP-Rpl10a mice were placed in an ethanol vapor chamber or in a control chamber for 4 hours a day from post-natal day 2 (PD2) to PD7. We analyzed mRNA expression in the pull-down fractions, containing astrocyte-specific RNA, and in the input fractions, containing total hippocampal RNA, by qPCR. We also analyzed the same genes in wild-type littermates of the transgenic animals. RNA expression of all laminin isoforms (α subunit-encoding *Lama1-5*; β subunit-encoding *Lamb1-3*, and γ subunit encoding *Lamc1*and 2), *Adamts1, 4, 5*and *9*, *Mmp14*and *15*, *Plat*, *Plau*, *Serpine1*, and *Dnmt1*, *3a*, and *3b*was analyzed. We identified genes that are enriched (*Plat, Plau*,*Mmp14*and *15, Adamts1*and *9, Lama2* and*5, Lamb2*,and*Lamc1*) or de-enriched (*Serpine1, Adamts4, Lama1* and*3, Lamc2,* and*Dnmt1*and *3a*) in astrocytes as well as genes that are expressed in astrocytes and in the whole hippocampus at similar levels (*Adamts5*, *Lama3* and*4*, and *Dnmt*3b). Furthermore, we identified genes that are selectively upregulated by ethanol in astrocytes (*Lama2, Lamc1,* and*Dnmt*3b) and genes that were upregulated only in the whole hippocampus (*Lama4, Lamb1,* and*Dnmt1*). *Plat* and *Adamts9*wereupregulated by ethanol in all the fractions. These results indicate that, during brain development, ethanol alters the expression of some genes in a cell-type specific manner. Notably, *Dnmt3b*, which is expressed in astrocytes and in the whole hippocampus at similar levels, is upregulated by ethanol selectively in astrocytes, indicating that ethanol may alter DNA methylation in this cell type differently than in other hippocampal cells.

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Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.16/C58

Topic: B.11. Glial Mechanisms

Support: Dana-Foundation "First in man" Clinical Neuroscience Award

Title: Novel A3 adenosine receptor agonist prolongs survival of human traumatized astrocytes

Authors: I.- . WANNER[1], A. KAMALI[1], T. LISTON[2], L. TAJALLI[1], D. HOLSTEIN[3], ***J. D. LECHLEITER**[4];
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Abstract: Adenosine is central in astrocyte communication and a major danger signal after traumatic brain injury (TBI). Mechanical shear and deformation of brain tissue causes cellular injury and ensuing cell death. Effective therapies for TBI are missing and translation of neuroprotective strategies lack sensitive pharmacodymanic biomarkers. We use an *in vitro*human trauma model to investigate a novel adenosine A3 receptor agonist, AST-004, to improve energy and ion homeostasis of wounded astrocytes (Wanner, IB 2012). Abrupt pressure-pulses injure cultured matured human astrocytes causing mechanoporation and progressive cell death (Halford J et al., 2017). Traumatized astrocytes were treated using a range of AST-004 doses. Integrity-compromise and cell death were identified by live-propidium iodine uptake, followed by cellular and released glial fibrillary acidic protein (GFAP) analyses. Automated microscope stage imaging and immunoblotting provided unbiased pharmacodynamic readout. Cells were counted using binarized images. PI-positive cell numbers increased significantly post-stretching (effect size 3). Stretched cultures treated with AST-004 had significantly reduced cell death versus untreated ones (effect sizes 3.3-3.5). Different cell death stages were assessed by scoring nuclear morphology. One-fifth of permeable cells displayed complete chromatin condensation or nuclear fragmentation, while the majority displayed earlier stages of cellular death. GFAP filament disassembly, breakdown and release correlated with human astrocyte injury and cell death (Halford et al., 2017). Stretching caused a significant increase in disassembled GFAP-bearing astrocytes with pyknotic nuclei (effect size 5.8). This population was significantly reduced by AST-004 (effect sizes 3.8-5). Immunoblotting confirmed GFAP release and breakdown changes. Disassembled GFAP fibers is known to associate with elevated intracellular calcium and subsequent calpain activation. Our data indicated that A3 receptor stimulation prevents compromised human astrocytes from progressing to cell death. Mouse brain injury and knockout studies support an underlying mechanism involving IP3-mediated release of calcium leading to increased mitochondrial energy levels (Parpura V. et al., 2017; Talley Watts L. et al., 2013). We conclude that AST-004 is a potent cytoprotective drug that shifts cell fates of traumatized human astrocytes towards survival and health. Future studies will address drug pharmacodynamics along with astroglial injury defined biomarker monitoring to guide therapeutic dosing for clinical use in TBI patients.

Disclosures: I. Wanner: None. **A. Kamali:** None. **T. Liston:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Astrocyte Pharmaceuticals inc.. **L. Tajalli:** None. **D. Holstein:** None. **J.D. Lechleiter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Astrocyte Pharmaceuticals inc..

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.17/C59

Topic: B.11. Glial Mechanisms

Support: Commonwealth of Virginia's ARDRAF Award No. 18-1

Title: Soluble oligomeric Aβ42 triggers degradation of the cerebrovascular basement membrane and disruption of the astrocyte-vascular interface

Authors: C. D. LIAO[1], A. STUBLEN[2], L. CHAUNSALI[1], H. SONTHEIMER[3], ***I. F. KIMBROUGH**[4];
[1]Fralin Biomed. Res. Inst. at VTC, Roanoke, VA; [2]Virginia Tech. Sch. of Neurosci., Blacksburg, VA; [3]Sch. of Med. and Res. Inst., Virginia Tech. Sch. of Neurosci., Roanoke, VA; [4]Sch. of Neurosci., Virginia Tech., Blacksburg, VA

Abstract: Astrocytes regulate local cerebral blood flow by communicating directly with vascular smooth muscle cells and pericytes. In Alzheimer's disease, a pathologic accumulation of amyloid along the vasculature (vascular amyloidosis) is a well-defined phenomenon. In a recent publication, we demonstrated loss of vascular regulation and astrocytic end-foot displacement in areas of vascular amyloid deposition. However, the pathogenic process through which the astrocyte-vasculature interaction is disrupted and whether end-foot disruption *precedes or follows* overt plaque deposition remains unclear.
Recent evidence suggests a role of *astrocytic* low density lipoprotein receptor-related protein (LRP1) and matrix metalloproteases (MMPs) in mediating the clearance of extracellular amyloid. We hypothesize that soluble, pre-plaque amyloid-beta oligomers (sAβO's) interact with astrocyte surface receptors such as LRP1, resulting in the release of MMPs that degrade the basement membrane, subsequently causing astrocytic end-foot displacement from blood vessels and reduced vascular integrity. After careful optimization and refinement of a protocol for the synthesis of sAβO's, we determined the effect of these oligomers on cultured astrocytes. *In vitro* data suggests that exposure to media containing varying concentrations of synthetic oligomeric Aβ42 causes astrocytes to undergo reactive gliosis, as indicated by increased GFAP staining. Interestingly, 24 hours after application to the culture medium and subsequent washing for analysis, oligomeric Aβ42 remains bound to the cultured astrocytes, suggesting significant binding affinity or intracellular compartmentalization. Additionally, we show that intracerebral injections of oligomeric Aβ42 result in amyloid-beta labeling throughout the hippocampal parenchyma with reduced polarization of astrocytic end-feet, diminished collagen IV and laminin expression around blood vessels in areas of higher Aβ42 density, and elevated LRP1 expression.

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Poster

468. Role of Astrocyte Dysfunction in Disease States

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.18/C60

Topic: B.11. Glial Mechanisms

Support: NIH NINDS R01NS094396

Title: *In vivo* spatiotemporal dynamics of astrocytes activity following neural electrode implantation

Authors: *S. P. SAVYA[1], S. WELLMAN[2], J. R. ELES[3], T. D. KOZAI[1];
[1]Bioengineering, [2]Dept. of Bioengineering, [3]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Intracortical microelectrode arrays have become invaluable tools for understanding neuronal function and neurodegenerative diseases due to their ability to communicate neuronal information. However, the use of such microelectrode arrays is limited as they are plagued with chronic instability due to inflammatory reactions, resulting in neuronal loss and glial cell encapsulation. Astrocytes have been well established as a key player during inflammation. With their unique ability to exhibit both pro- and anti-inflammatory mechanisms, they can exert different behaviors in a context-dependent manner - temporally after injury or spatially relative to the lesion. Previous studies have used post-mortem immunohistochemistry to uncover glial responses in relation to chronic electrode implants. Unfortunately, these methods limit cellular dynamics during acute inflammation. Here, we utilize two-photon microscopy to show the spatiotemporal dynamics of fluorescently-labeled astrocytes after insertion of a microelectrode array in the mouse cortex. Early results show astrocytes initiating processes extension 40 min after implantation (0.05um/min). In addition, there are very few astrocytes 6 h post-insertion that initiate soma migration towards the area of tissue damage, with more distant astrocytes (~170um from probe surface) migrating at 72 h. This suggests astrocytes activate subsequently to microglia activation, yet prior to other cells such as oligodendrocyte precursor cells (OPC). Astrocytes also begin to increase in volume 24h after implantation, contributing to vasculature dilation and reorganization. By highlighting and identifying novel patterns of astrocytic activity, the stability and longevity of neural implants may improve due to the development of therapeutic strategies to attenuate the immune response.

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Poster

468. Role of Astrocyte Dysfunction in Disease States

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Program #/Poster #: 468.19/C61

Topic: B.11. Glial Mechanisms

Support: DA041751
DA043164
MH112848
DA040397
DA043138

Title: Role of HIF-1α-lncRNA BACE1-antisense complex in HIV-1 Tat mediated induction of astrocytic amyloidogenesis

Authors: *S. SIL, G. HU, K. LIAO, S. CALLEN, S. BUCH;
Univ. of Nebraska Med. Ctr., Omaha, NE

Abstract: Increased life expectancy of HIV^+ patients in the era of combined anti-retroviral therapy (cART) is paradoxically also accompanied by increased prevalence of HIV-associated neurological disorders (HAND) and comorbidities such as Alzheimer's Disease (AD). It is now well recognized that despite effective cART-mediated suppression of viremia in the periphery, lack of penetration of some of the cART regimens across the blood-brain barrier, often results in persistent low-level viral replication in the CNS and accumulation of cytotoxic viral proteins such as transactivator of transcription (Tat). While there are reports on Tat-mediated production of the toxic amyloid protein by neurons, the role of astrocytes as potential contributors of amyloidogenesis remains less explored. The present study was thus undertaken to assess the role of HIV Tat in mediating astrocytic amyloidogenesis, which, in turn, could also have a significant deleterious effect on the neurotoxicity associated with HAND. Our *ex vivo* findings in the autopsied brains sections of that SIV^+ macaques & HIV^+ patients with differential cognitive status, identified brain region specific upregulation of the amyloidogenic components that co-localized with GFAP positive astrocytes. Furthermore, in the cell culture studies Tat-mediated amyloidogenesis correlated with upregulation of Alzhemier's associated markers such as BACE-1, amyloid precursor protein (APP), AβmOC64, p-Tau, as well as increased activity of BACE-1 in human primary astrocytes (HPA) exposed to Tat. Molecular mechanism(s) underlying this process involved upregulation of hypoxia inducible factor (HIF-1α), its translocation to the nucleus & its binding to the long noncoding (lnc) RNA BACE-1AS, resulting in formation of an unique complex that was validated by RNA immunoprecipitation assay and Electrophoretic Mobility Shift Assay. Furthermore, Chromatin Immunoprecipitation Assay identified functional binding of the complex to BACE-1 promoter, leading in turn, to increased expression of BACE-1

that involved transcriptional, post transcriptional & translational mechanisms as well as its increased activity resulting in increased cleavage of APP to its toxic Aβ-42 form. Gene silencing approaches further confirmed the regulatory role of HIF-1α-lncRNA BACE-1AS axis in generation of Aβ. This is the first report demonstrating the mechanism by which the HIV viral protein Tat induces HIV-associated astrocytic amyloidogenesis. Further this complex of HIF-1α-lncRNA BACE-1AS can be targeted to develop adjunctive therapy for HIV^+ subjects on cART therapy.

Disclosures: **S. Sil:** None. **G. Hu:** None. **K. Liao:** None. **S. Callen:** None. **S. Buch:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.20/C62

Topic: B.11. Glial Mechanisms

Support: NIDA T32 DA007244
NIDA R01 DA034721

Title: Neuroimmune consequences of heroin withdrawal on stress enhanced fear learning

Authors: *S. V. PAREKH, J. E. PANICCIA, C. L. LEBONVILLE, D. LYSLE;
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Abstract: Converging evidence suggests opioid abuse leads to increased incidence and severity of post-traumatic stress disorder (PTSD) in clinical populations. For example, heroin use is associated with increased anxiety and severity of PTSD symptoms, while opioid withdrawal produces similar symptoms to those of PTSD. This relationship suggests the possibility of a common underlying neurobiological mechanism of opioid withdrawal and PTSD. Our laboratory has investigated the mechanism of stress enhanced fear learning (SEFL), an animal model of PTSD. We have established that the severe stressor in the SEFL paradigm induces a time-dependent, region-specific increase in dorsal hippocampal (DH) interleukin-1β (IL-1β). Additionally, we have discovered the primary source of this stress-induced DH IL-1β increase is in DH astrocytes. This IL-1 signaling is critical to the establishment of a PTSD-like phenotype, as site-specific antagonism of DH IL-1 signaling abolishes SEFL. To begin to understand more about the relationship between PTSD and heroin withdrawal as well as examine if similar underlying neural mechanisms are involved in heroin withdrawal and SEFL, our laboratory conducted two sets of experiments. The first set of experiments used a chronic escalating heroin dose and withdrawal paradigm to substitute for the severe stressor in the SEFL model to examine whether withdrawal or a history of chronic heroin would be a comparable stressor. The results showed escalating heroin administration followed by withdrawal can substitute for a severe

stressor in the SEFL model in that both severely stressed and heroin withdrawn animals exhibited enhanced freezing levels on Test Day 2 compared to controls. The second set of experiments aimed to explore whether cytokines, specifically IL-1β, were involved in this withdrawal behavior. Protein analysis of IL-1β and glial fibrillary acidic protein (GFAP), a marker of astrocyte reactivity, following a twenty-four-hour withdrawal revealed there were increases in both. Together, these studies provide the first set of evidence that heroin withdrawal may act as a severe stressor in SEFL, produce a PTSD-like phenotype in an animal model, and hippocampal IL-1β signaling may play a critical role in heroin withdrawal and the development of PTSD.

Disclosures: S.V. Parekh: None. **J.E. Paniccia:** None. **C.L. Lebonville:** None. **D. Lysle:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.21/C63

Topic: B.11. Glial Mechanisms

Title: Dexamethasone modifies expression of the five subtypes of dopamine receptors in C6 glioma cells

Authors: *N. LÓPEZ-AMADOR, F. PAZ-BERMUDEZ, A. ÁVALOS-FUENTES, A. NAVARRETE-ALONSO, P. VERGARA-ZUBILLAGA, J. SEGOVIA-VILA, B. FLORÁN-GARDUÑO;
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Abstract: Background: Previous works have demonstrated that glucocorticoids modify the expression and signaling of certain metabotropic receptors, but sparse evidence is available regarding their effects on dopamine receptors. Recent data on the function of dopaminergic receptors expressed in astrocytes, indicates their important role modulating neuroinflammation and neuroprotection. **Objective**: The main objective of this work is to elucidate the effect of glucocorticoids on the expression of dopamine receptors in glial cells. **Methods**: Cultured C6 glioma cells were treated with dexamethasone in serum-free medium. The glucocorticoid receptor antagonist, mifepristone (RU486), was used as a control to prevent the effect of dexamethasone. Basal expression of the 5 subtypes of dopamine receptors was detected by immunofluorescence. Changes in the expression of dopamine receptors, induced by dexamethasone, were detected by western blotting. Relative densities of luminescence signals were quantified using Image J software. ANOVA with Tukey's post-hoc test was applied to analyze results. **Results**: In C6 glioma cells, the expression levels of dopamine receptors D1

(n=3; p=0.0014), D3 (n=4; p=0.003) and D4 (n=2; p=0.0166) were downregulated by dexamethasone, while dopamine receptors D2 (n=2; p=0.003) and D5 (n=2; p=0.0118) were upregulated, compared with non-treated controls. Remarkably, D2 receptor expression was induced more than 3-fold, compared with controls. **Conclusions**: We demonstrated that the expression of the five subtypes of dopamine receptors can be regulated by glucocorticoids. These results are relevant to obtain a better understanding of the underlying mechanisms in astrocyte response to stress, neuroinflammation and the putative role of glucocorticoids on dopaminergic function. Further investigation could define the effects of glucocorticoid on dopaminergic signaling. This research line may be important to develop novel therapeutic approaches in neurodegenerative disease.

Disclosures: N. López-Amador: None. **F. Paz-Bermudez:** None. **A. Ávalos-Fuentes:** None. **A. Navarrete-Alonso:** None. **P. Vergara-Zubillaga:** None. **J. Segovia-Vila:** None. **B. Florán-Garduño:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.22/C64

Topic: B.11. Glial Mechanisms

Support: NIH Grant DA040397
NIH Grant DA042704
NIH Gran DA046831

Title: Morphine-mediated release of astrocyte-derived extracellular vesicle miR-23a induces loss of pericyte coverage at the blood-brain barrier: Implications for neuroinflammation

Authors: *K. LIAO, F. NIU, G. HU, S. SIL, S. BUCH;
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Abstract: Opioids such as morphine (Mor) are the most potent and efficacious drugs currently available for pain management. Paradoxically, however, opioids have also been implicated in impairing neurocognition likely via breaching the blood-brain barrier (BBB). Pericytes are key players in the maintenance and functioning of BBB. Our previous study has demonstrated that extracellular vesicles (EVs) released from Mor-exposed astrocytes can exert dysfunction of microglial phagocytosis involving activation of TLR7 signaling. The current study was undertaken to examine the effect of miRNAs in the Mor-stimulated astrocyte EV cargo in mediating pericyte loss at the BBB, leading, in turn, to increased influx of peripheral monocytes. Astrocyte-derived-EVs (ADEVs) were purified from control or Mor-exposed astrocytes using the standard differential ultracentrifugation technique followed by characterization using western

blot, transmission electron microscopy, atomic force microscopy and NanoSight analyses. Functional endpoints included assessment of pericyte migration using Boyden chamber, wound healing assays and the endothelial-pericyte 3D co-culture model. Our findings suggested that induction of miR-23a involved signaling via the mu opioid receptor and, furthermore, that the heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNP A2/B1) played a role in the sorting of miR-23a in the EVs. Pharmacological and gene silencing approaches were used to validate these findings. The migration of pericyte involved down-regulation of the miR-23a target- PTEN, which was further validated by overexpressing PTEN or transfecting miR-23a-PTEN target protector in pericytes to attenuate Mor-ADEVs-mediated pericyte migration. Validation of decreased pericyte coverage was also demonstrated *ex vivo*, wherein lesser PDGFβR+ pericytes were found to co-localize with CD31+ brain endothelial cells in microvessels isolated from Mor-administrated mice. In line with these observations and of importance, we also observed increased loss of pericytes and a concomitantly increased influx of monocytes in sections of brains from pericyte-labeled NG2-DsRed mice that were administered Mor for 7 days. In conclusion, our findings indicate that in the brain Mor-mediated dysregulation of miRNA expression in the astrocytes involves cellular crosstalk with the pericytes via the EVs, leading to loss of pericyte coverage at the brain endothelium with increased influx of peripheral monocytes leading to neuroinflammation.

Disclosures: **K. Liao:** None. **F. Niu:** None. **G. Hu:** None. **S. Sil:** None. **S. Buch:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.23/C65

Topic: B.11. Glial Mechanisms

Support: NIH Grant DA041455
NIH Grant DA044695

Title: Sex differences in the structural plasticity of nucleus accumbens astrocytes associated with the incubation of cocaine craving

Authors: *R. KIM[1], N. E. BROWN[1], A. TESTEN[2], E. A. WILLIAMS[1], K. J. REISSNER[1,2]; [1]Psychology and Neurosci., Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [2]Neurosci. Curriculum, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Astrocytes play critical roles in many processes in both health and disease. As such, structural and physiological adaptations in astrocytes have been implicated in neuropsychiatric diseases including drug addiction. Previously, we showed that following short-access (ShA, 2-hours/day) cocaine self-administration and extinction training, astrocytes in the nucleus

accumbens (NAc) exhibit a decrease in surface area, volume and synaptic colocalization (Scofield et al., 2016; Testen et al., 2018). However, it is unknown whether similar effects would be observed in other preclinical models of drug addiction, such as the incubation of cocaine craving model. Incubation of drug craving refers to an increase in behavioral measures of drug seeking across abstinence, and is characterized by a number of cellular adaptations in the NAc (Wolf, 2016). Among these, prolonged abstinence is associated with an increased magnitude of suppression of the astrocytic glutamate transporter GLT-1 protein, as well as genetic downregulation of the GLT-1 gene (Fischer-Smith et al., 2012; Kim et al., 2018). Furthermore, the effects of cocaine self-administration on NAc astrocytes have not been investigated in female rats. To address these questions, high resolution confocal imaging of NAc astrocytes was performed using an AAV5-Lck-GFP virus under the control of an astrocyte-specific promoter in both male and female rats, following the parameters often used in the incubation of cocaine craving: long-access (LgA, 6-hours/day) cocaine self-administration followed by 45 days of abstinence. Results indicate that following this protocol, astrocytes in the NAc of male rats show marked decreases in surface area, volume and colocalization with the post-synaptic marker PSD-95. However, these changes in NAc astrocytes were not observed in female rats. These results indicate sex differences in the cocaine-induced changes in astrocytes. In male rats, NAc astrocytes exist in an atrophic state following prolonged abstinence from LgA cocaine self-administration. This retracted phenotype signifies a cellular adaptation that occurs during abstinence and represents a potential mechanism for the incubation of craving. However, in female rats, other mechanisms and cellular adaptations may contribute to the incubation of cocaine craving.

Disclosures: R. Kim: None. **N.E. Brown:** None. **A. Testen:** None. **E.A. Williams:** None. **K.J. Reissner:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.24/C66

Topic: B.11. Glial Mechanisms

Support: 5R01DA041455-04

Title: Branching plasticity of nucleus accumbens astrocytes following cocaine self-administration

Authors: *A. TESTEN[1], H. WANG[2], R. KIM[2], M. J. GASTINGER[3], K. J. REISSNER[1,2]; [1]Neurosci. Curriculum, [2]Dept. of Psychology and Neurosci., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Bitplane, Concord, MA

Abstract: Astrocytes are critical players in the maintenance of brain homeostasis via intricate structural interactions with vascular and synaptic elements. These interactions are maintained by fine peripheral astrocytic processes (PAPs) which must dynamically adapt to changes to the local environment, making astrocytes exceptionally plastic. Neurological disorders and substance use disorders are both characterized by imbalances of brain homeostasis, due in part to impaired astrocyte function. However, the impact of these disorders on astrocyte structural plasticity is not well understood. Previously we showed that astrocyte surface area and colocalization with synaptic elements are markedly decreased in the nucleus accumbens from rats after short-access (2h/day) cocaine self-administration and extinction training (Scofield *et al.*, 2016; Testen *et al.*, 2018). These changes are also robustly observed after long-access (6 h/day) self-administration followed by 45 days of forced abstinence (Kim *et al*., unpublished data, linked poster). Abstinence from cocaine thus reproducibly results in a retracted phenotype of accumbal astrocytes, evidenced by decreases in surface area and synaptic colocalization. It is not clear however, if the retracted phenotype is also associated with any quantitative and/or qualitative changes in astrocyte branching pattern, or if this is a consequence of overall shrinkage of PAPs. To this end, branching pattern analysis of previously acquired astrocytes was performed. Astrocytes were reconstructed in 3D and their processes traced in order to construct a high-fidelity wire model using a fast-marching algorithm (Sethian, 1996), powered by Imaris software. Individual wire models were then analyzed by a custom-made MATLAB script, capable of mapping and classifying individual branching nodes as well as performing Scholl analysis. Results show decreased branching complexity of individual astrocytes associated with the short-access/extinction paradigm, which is further deteriorated in the long-access/abstinence paradigm. Scholl analysis on the other hand shows a distinct difference in intersection patterns produced by both self-administration paradigms. Interestingly, the length of individual branch segments (from node to node) remain unaffected by cocaine in either paradigm. In summary, the retracted phenotype of accumbal astrocytes following cocaine self-administration and extinction or abstinence appears not due to simple shrinkage of existing astrocytic processes, but is characterized by remodeling of branching complexity.

Disclosures: **A. Testen:** None. **H. Wang:** None. **R. Kim:** None. **M.J. Gastinger:** None. **K.J. Reissner:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.25/C67

Topic: B.11. Glial Mechanisms

Support: HI14C1913
NRF-2016R1E1A1A01941212

2017M3C7A1028949
2017R1D1A1B05028221

Title: Cilostazol restores autophagy flux in bafilomycin A1-treated cultured cortical astrocytes by lysosomal reacidification: Roles of PKA, zinc and metallothionein 3

Authors: *H. KIM[1], B.-R. SEO[1], J. CHOI[1], Y. YOON[2], J.-Y. KOH[3];
[1]Neural Injury Res. Ctr., Asan Inst. For Life Sci., Seoul, Korea, Republic of; [2]Ophthalmology, [3]Neurol., Asan Med. Ctr., Seoul, Korea, Republic of

Abstract: In many neurodegenerative diseases such as Alzheimer disease (AD), lysosomal dysfunction may be a common underlying pathogenic mechanism. While cilostazol, a PDE3 inhibitor/anti-platelet agent, reduces amyloid burden in mouse models of AD, its mechanism has not yet been clarified. In the present study, using cultured cortical astrocytes, we examined the possibility that cilostazol ameliorates lysosomal dysfunction induced by bafilomycin A1 (BA), an inhibitor of lysosomal v-ATPase.To estimate lysosomal pH, cortical astrocytes were loaded with DND189 or acridine orange. Compared to sham wash controls, astrocytes treated with BA for 60 min exhibited reduced lysosomal acidity. In both cases, BA-induced pH changes were reversed by cilostazol, dibutyryl cAMP, or a PKA activator forskolin. Conversely a PKA inhibitor H-89 blocked the effect of cilostazol or cAMP. Then, we examined whether the cilostazol/cAMP/PKA effect was mediated by increases in free zinc levels. FluoZin3 fluorescence showed that all significantly increased intracellular free zinc levels particularly in lysosomes. Addition of TPEN not only blocked the zinc increase, but also abrogated lysosomal acidification in all cases. Indicating that the zinc rises in astrocytes were mainly from MT3, dibutyryl cAMP or forskolin treatment failed to raise free zinc levels in MT3 null astrocytes. Furthermore, addition of dibutyryl cAMP or forskolin failed to reverse BA-mediated lysosomal alkalization in MT3 null astrocytes. Present results present a novel finding that cAMP/PKA can overcome the v-ATPase blocking effect of BA in a zinc- and MT3-dependent manner. The fact that cAMP/PKA can re-acidify lysosomes in the presence of a potent inhibitor of v-ATPase, suggests the possibility of an alternate, zinc-dependent pathway for lysosomal acidification.

Disclosures: H. Kim: None. **B. Seo:** None. **J. Choi:** None. **Y. Yoon:** None. **J. Koh:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.26/C68

Topic: B.11. Glial Mechanisms

Support: HI14C1913
NRF-2016R1E1A1A01941212

2017M3C7A1028949
2017R1D1A1B05028221

Title: Cyclic AMP and PKA overcomes bafilomycin A1-induced lysosomal alkalinization in cortical astrocytes: A possible role of ATP4B, a potassium/hydrogen pump

Authors: *H. LEE[1], Y. YOON[2], J.-Y. KOH[3];
[1]ASAN Med.Center, Seoul, Korea, Republic of; [2]Ophthalmology, Asan Med. Ctr., SEOUL, Korea, Republic of; [3]Univ. Ulsan Col. Med., Seoul-City, Korea, Republic of

Abstract: Vacuolar ATPase (v-ATPase) is the main proton pump to acidify autophagosomes and lysosomes. Its mutations and/or failure of lysosomal localization cause defective lysosomal acidification and autophagy/lysosomal dysfunction, thus contributing to the pathogenesis of lysosomal storage disorders (LSDs) and common neurodegenerative diseases like Alzheimer's disease (AD). Recent studies showed that increases in cAMP levels, directly with db-cAMP or by the action of PDE inhibitors, help acidify lysosomes under certain circumstances and consequently enhance autophagy flux. While upregulation of v-ATPase function may be the key mechanism to lysosomal acidification, we examined the possibility that v-ATPase-independent mechanism is additionally at play, using cultured mouse cortical astrocytes. We first examined effects of cAMP on lysosomal acidification under autophagy-arrested (bafilomycin A1-treated) condition in astrocytes using LysoSensor DND-189, a pH-sensitive fluoroprobe. Compared with lysosomes of sham washed control astrocytes, those of db-cAMP treated astrocytes exhibited more intense fluorescence in accordance with increased acidification even in the presence of bafilomycin A1, a potent yet selective inhibitor of v-ATPase. Furthermore, as a consequence, autophagy flux was increased as evidenced by decreases in the level of LC3-II and p62. To find possible mechanisms of lysosomal acidification that may have bypassed v-ATPase activity, we examined whether another kind of proton pump activity was involved. Since H^+/K^+ ATPase (HK -ATPase) has been found to be associated with lysosomes in certain cases (*Andonian S et al., Mol Reprod Dev. 2001*), we tested omeperazole (OPZ) and lansoparazole (LPZ), inhibitors of HK-ATPase. While neither changed lysosomal pH in control astrocytes indicating minimal role of HK ATPase herein, OPZ or LPZ markedly shifted lysosmal pH to the alkaline direction in bafilomycin A1/db-cAMP-treated astrocytes. Moreover, Western blots showed that db-cAMP treatment substantially increased the level of ATP4B, a subunit of HK -ATPase, and increases its recruitment to lysosomes. Pending further experiments, our results suggest that HK-ATPase may be able to act as a second line proton pump for lysosomes, especially in case of v-ATPase dysfunction. It is intriguing that HK-ATPase induction and lysosomal recruitment appear under the control of cAMP/PKA, which finding may provide new insights into the development of a new class of lysosome-targeted therapeutics.

Disclosures: **H. Lee:** None. **Y. Yoon:** None. **J. Koh:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.27/C69

Topic: B.11. Glial Mechanisms

Support: NIH/NIA 1R01AG059639
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Alzheimer's Association Grant 591887
Showalter CTSI investigator award
Indiana Alzheimer Disease Center pilot project
Research Supplement to Promote Diversity in Health-Related Research (PA-18-906)

Title: Synaptic alterations induced by amyloid-beta stimulated astrocytes are tau dependant

Authors: *P. CISTERNAS, X. TAYLOR, A. PERKINS, C. LASAGNA-REEVES;
Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Alzheimer's disease (AD) is a neurological disorder exhibiting loss of cognitive functions, molecularly characterized by the overproduction and accumulation of amyloid-beta (Aβ), followed by intraneuronal aggregation of tau. These events induce astrogliosis and leads to extensive neuronal death. Aβ originates in the neuron and its accumulation precedes tau pathology. On the other hand, tau is necessary for Aβ to exert its neurotoxicity and propagates between neurons at synapses, inducing its aggregation. This evidence situates neurons and synapses as central players in the propagation of tauopathy. However, there are no studies addressing in detail the role of astrocytes in these events, being a key component of synapses. Our goal is to understand the astrocyte-neuron axis from an Aβ-tau perspective and evaluate astrocytes as a new cellular player in neurotoxicity. We used an *in vitro* approach to answer this question. We induced astrogliosis in wt and $tau^{-/-}$ astrocytes adding exogenous recombinant Aβ and measured the amount of tau oligomers secreted in the media. We found an increase in tau oligomers in an Aβ concentration-dependent fashion. To evaluate the neuroprotective effects of tau ablation on astrocytes, we co-cultured neurons with Aβ-stimulated wt and $tau^{-/-}$ astrocytes. In these neurons we assessed synaptic organization by immunofluorescence and western blot, quantifying the number positive ((+)) clusters and the amount of synaptic markers synapsin-1 and PS95 respectively. We evaluated the functioning of the synapse by quantifying the number of CamKII-(+) spines through immunofluorescence. We also evaluated the extent of neuronal death by western blot for apoptosis marker caspase-3. Neurons co-cultured with wt-stimulated astrocytes showed a decrease in both (+) clusters and amount of synaptic markers. They also showed a decrease in the number of (+) CamKII spines, and an increase in caspase-3 amount.

These effects were not present on neurons co-cultured with tau$^{-/-}$-stimulated astrocytes. These results show that astrocytic tau oligomers are necessary for Aβ to exert its neurotoxicity, and that removing astrocytic-tau from astrocytes prevents synaptic degeneration and neurotoxicity. Dissecting the mechanism by which Aβ exerts its neurotoxic effect via tau and identifying new cellular interplays of molecular components in AD will contribute to formulating strategies for managing this disease.

Disclosures: P. Cisternas: None. **X. Taylor:** None. **A. Perkins:** None. **C. Lasagna-Reeves:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

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Program #/Poster #: 468.28/C70

Topic: B.11. Glial Mechanisms

Support: 2017M3C7A1028949
HI14C1913
2017R1D1A1B05028221
NRF-2016R1E1A1A01941212

Title: Zinc dyshomeostasis contributes to inflammasome formation induced by LPS or OGD exposure in cortical cell culture

Authors: *H.-S. PARK[1], Y. YOON[2], J.-Y. KOH[3];
[1]Asan Inst. For Life Sci., Seoul, Korea, Republic of; [2]Ophthalmology, Asan Med. Ctr., SEOUL, Korea, Republic of; [3]Univ. Ulsan Col. Med., Seoul-City, Korea, Republic of

Abstract: Following acute brain insults such as ischemia and trauma, neurons and astrocytes form inflammasomes. If excessive, thus formed inflammasomes may contribute to the further propagation of brain injury. Since zinc dyshomeostasis is implicated in brain injury as well as inflammation, in the present study, we examined whether zinc dyshomeostasis contributes to inflammasome formation in cultured cortical cells.In mouse cortical cell cultures, exposure to LPS induced inflammasomes, as indicated by increases in the level of NLRP3, ASC, caspase-1 and IL1β by western blot assay and immunocytochemistry. Concurrently, LPS increased levels of free zinc in neurons and astrocytes. Indicating that rises zinc levels play a role in inflammasome formation, the membrane-permeant zinc chelator TPEN blocked the increase in levels of NLRP3 and caspase-1, as well as the release of inflammatory cytokines into the media. Similar changes were observed in OGD in cortical cultures, a cell model for ischemia. First, OGD induced zinc dyshomeostasis and inflammasome formation. Second, modulation of zinc levels altered the extent of inflammasome formation. Finally, we injected LPS in mice and

examined the brain. Inflammasome formation and microglial activation were induced by LPS. In ZnT3 null mice, which have no synaptic zinc in the brain, LPS induced much reduced inflammasome formation. Combined with the finding that LPS treatment acutely reduced the level of synaptic zinc, this result suggests that release of synaptic zinc may play a role in LPS-induced inflammasome formation.The present study showed that zinc dyshomeostasis, partly caused by synaptic zinc release, plays a role in inflammasome formation in neurons and astrocytes induced by LPS and OGD. In light of evidence that inflammasome formation may contribute to the expansion of brain injury in ischemia, understanding the mechanism of zinc dyshomeostasis and its suppression may help reduce inflammation-related secondary brain injury.

Disclosures: **H. Park:** None. **Y. Yoon:** None. **J. Koh:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.29/C71

Topic: B.11. Glial Mechanisms

Support: NIH DA0044782

Title: Morphological plasticity of astrocytes in the ventral pallidum after heroin self-administration

Authors: *A. KRUYER, P. W. KALIVAS;
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Abstract: GABAergic projections from the nucleus accumbens core (NAcore) to the dorsolateral ventral pallidum (dlVP) are necessary for reinstated cocaine seeking induced by cocaine-associated cues. While the dlVP receives input from both D1 and D2 receptor expressing neuronal subtypes, D2 projections to the dlVP inhibit motivated behavior and exhibit reduced plasticity after chronic cocaine use. Astrocytes are capable of uptake and release of both GABA and glutamate and are therefore capable of modulating synaptic physiology and astrocytes in the NAcore attenuate drug seeking induced by cues. In order to study the contribution of astrocytes to synaptic plasticity in downstream structures, we labeled astrocytes in the dlVP and examined astroglial proximity to D1 or D2 terminals, as well as surface expression of the GABA transporter GAT-3 using confocal microscopy. Astroglial adaptations after extinction from heroin self-administration and in response to cues that predict heroin delivery are presented here along with a discussion of the contribution these adaptations would be expected to have on synaptic plasticity in the dlVP.

Disclosures: **A. Kruyer:** None. **P.W. Kalivas:** None.

Poster

468. Role of Astrocyte Dysfunction in Disease States

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 468.30/C72

Topic: B.11. Glial Mechanisms

Title: Induction and characterization of human A1 astrocytes

Authors: *H. KOBAYASHI[1], A. NABETANI[1], H. SUZUKI[1], W. SHIN[1], K. MAEDA[2], K. KAZETANI[2], T. WAKUI[2], J. HOSOKAWA[1], S. ENDOH-YAMAGAMI[1];
[1]Bio Sci. & Engin. Lab., [2]Imaging Technol. Ctr., FUJIFILM Corp., Kanagawa, Japan

Abstract: Astrocytes, the most abundant population of the glial cells, are essential for neuronal survival and functions. Recently, increasing number of studies show that astrocytes are also involved in various neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. Recently, the presence of two reactive astrocyte subpopulations was reported: neuroprotective A2 and neurotoxic A1 astrocytes. Increased number of A1 astrocytes are observed in the brains from patients of human neurodegenerative diseases, and A1 astrocytes are getting attention as a novel target for treatment of these diseases. In this study, we established a method to generate A1 astrocytes in vitro using human iPSC-derived astrocytes. The popular method to generate astrocytes from stem cells uses FBS stimulation. However, it has been reported that serum exposure alters the properties and functions of astrocytes in culture. Therefore, all of our experiments were performed under the condition without serum. At first, we stimulated human astrocytes with the A1-inducing condition reported in rodent primary cells. However, we could not recognize the induction of strong neurotoxicity. Then, we examined several conditions to stimulate human astrocytes and evaluated the neurotoxicity. As a result, we found a condition to induce strong neurotoxic A1 phenotype using human astrocytes. The astrocytes stimulated under the condition showed increased A1 maker expression and hypertrophic morphology. These results suggested that the condition inducing A1 astrocytes has species specificity between mouse and human.
The human A1 astrocytes reported here will provide a beneficial tool to develop the new therapeutic agents for neurodegenerative diseases.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.01/C73

Topic: B.11. Glial Mechanisms

Support: NIH grants DC000407

Title: Microglia and their role in the pruning of gustatory nerves afferent terminal fields in the mouse NST

Authors: *C. SUN[1], F. KONG[2], D. L. HILL[1];
[1]Psychology, Univ. Virginia, Charlottesville, VA; [2]Binzhou Med. Col., Yantai, China

Abstract: Age-related decreases in terminal field sizes occur in a variety of sensory systems. We found that this also occurs in the developing gustatory system. The terminal fields of the mouse chorda tympani (CT) and greater superficial petrosal (GSP) nerves in the nucleus of the solitary tract (NST) decrease (i.e., "pruned") approximately 2X from postnatal day 20 (P20) to P30. The terminal field size of the IX does not change with age. By contrast, mice born to mothers fed a Na^+-restricted diet only from embryonic day 3 (E3) to E12 show a failure to prune: the terminal fields in adult Na^+-restricted mice resemble those of young, control mice. We identified the Classical Complement Cascade as a potential pruning mechanism in control mice. This cascade involves reciprocal signaling between terminals/synapses (i.e., taste afferents) and the immune system (i.e., microglia). To directly address the role of microglia in gustatory circuit development, we asked if attenuating microglia function in postnatal control mice leads to a failure to prune terminal fields, or conversely, if augmenting microglia function in postnatal E3-E12 Na^+-restricted mice induces pruning. Through daily injections of minocycline from P15-P40 in control mice or eliminating microglia by feeding control mice PLX5622 from P20-P40, the CT and GSP terminal field volumes were 70%-80% greater than their untreated littermates—they failed to prune. Conversely, through injections of macrophage colony stimulating factor (m-csf) every 3 days from P10-P40, the CT and GSP terminal field volumes in E3-E12 Na^+-restricted mice were 40%-60% less than their untreated littermates—pruning was induced. These findings provide direct evidence of the involvement of microglia in the maturation of central gustatory circuits, and highlight the high degree of plasticity in the circuit that provides direct gustatory input to the brain.

Disclosures: C. Sun: None. **D.L. Hill:** None. **F. Kong:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.02/C74

Topic: B.11. Glial Mechanisms

Title: Differential phenotypic effects of hemin on murine and human microglial cell lines

Authors: V. BOINPELLY[1], A. ALEMIFAR[1], J. ZHOU[1], R. SHARMA[1], M. SHARMA[1], ***V. SINGH**[2,1];
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Abstract: Introduction: Dysregulation of iron homeostasis with consequent iron accumulation in the neuropil has been implicated as a major contributor to brain pathology in ageing and neurodegenerative disorders. Microglia serve diverse roles in multiple processes including inflammation, cellular energetics and synaptic pruning. Many groups have shown toxic effects of hemin on microglia with microglial morphology being considered a strong indicator of the functional state of microglia. However, literature review shows wide variations in hemin doses used for studies on murine and human derived microglial cell lines. **Aims:** To study the effects of various concentrations of hemin on morphology of mouse (BV2) and human (HMC3) microglial cell lines. **Methods:** BV2 and HMC3 (ATCC #CRL3304; embryonic microglia, clone 3; Lot # 70006081) were used. After preliminary experiments, hemin was used at 10 to 500 µM concentrations, in line with those previously reported. Light and fluorescence microscopy to assess cell morphological changes, LDH release assay for cytotoxicity, MTT assay for cell proliferation at various time points and RT-qPCR for gene expression were used. **Results:** Light microscopy showed a robust response of HMC3 cells to hemin (10-50 µM) with change in morphology from arborized (resting) to rounded phenotype with retracted processes which is considered to be an activated microglial phenotype. In contrast, BV2 cell morphology altered only at 250 and 500 µM hemin. Immunofluorescence microscopy showed that hemin (50 µM) upregulated the expression of IBA1 protein. RT-qPCR showed increased gene expression of CD40 at 6h and 24h ($P< 0.0214$) and increased expression of CD68 24h ($P<0.0042$) but not at 6h. Increased levels of IBA1, CD40 and CD68 are considered as markers of microglial activation. MTT assay showed that brief treatment (2h) with 50 µM hemin ($P<0.002$) or longer treatment (24h) with 1 µM hemin ($P<0.0001$) caused significant attenuation of HMC3 proliferation. Hemin at 50 µM was cytotoxic within 2h ($P<0.009$) determined by LDH release. This corresponds to results from other studies showing 60-70% human glial cell death by 3-30 µM hemin. **Conclusion:** The dose of hemin required to induce microglial activation and cell death was much lower in HMC3 cell as compared to BV2 cells. Differential dose response of

murine and human microglial cells to hemin significant implications for future research to study the role of microglia in neurodegeneration associated with iron accumulation.

Disclosures: **V. Singh:** None. **V. Boinpelly:** None. **A. Alemifar:** None. **J. Zhou:** None. **R. Sharma:** None. **M. Sharma:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

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Program #/Poster #: 469.03/C75

Topic: B.11. Glial Mechanisms

Support: Grant BFU2015-66941R from Spain's Ministerio de Economía y Competitividad / Fondo Europeo para el Desarrollo Regional (MINECO/FEDER)

Title: Multiple morphometric assessment of the microglial cell population in the deafferented spinal trigeminal nucleus

Authors: N. GARCÍA-MAGRO[1], ***P. NEGREDO**[1], Y. MARTIN[2], C. AVENDANO[3]; [1]Univ. Autónoma de Madrid, Madrid, Spain; [2]Francisco de Vitoria Univ. CIF – G80480197, Pozuelo de Alarcon, Spain; [3]Univ. Autonoma de Madrid, Fac. Medicina, Madrid, Spain

Abstract: Microglial cells (MC) in primary sensory territories react promptly to deafferentation by peripheral nerve injury by proliferating, migrating, and changing their structure from a 'resting' to a dynamic 'activated' state. This reaction is primarily associated to the phagocytic role of MC in the removal of cellular debris that ensue denervation. Moreover, when injury brings about a persistent painful condition, the activated MC release signaling molecules and modulates the activity of neighboring neurons, playing a significant role in the development and chronification of neuropathic pain. A variety of parameters has been used to characterize immunolabeled MC, most notably their number, cell soma size, length and complexity of processes, and various topological features. However, unbiased measurements of MC populations have proved hard to obtain. In most cases, selected MC in histological sections are reconstructed with digital tracking software (Imaris, Neurolucida), but completeness of cell labeling and unbiased cell sampling is not always insured. Other studies rely on image analysis (skeletonization and/or segmentation with, e.g., Imaris or Fiji), which is unduly sensitive to multisize, high density, and wide-range luminance profiles. In this work we present an efficient multiple stereological approach to get population data of MC on cell number, soma size and average length of processes in a region with different immunolabeling procedures. This analysis was carried out in the infraorbital nerve (IoN)-innervated region of the caudal spinal trigeminal and upper cervical dorsal horn, in control and IoN-transected C57BL/6 mice. Alternate coronal sections were immunostained with rabbit α-Iba1 (Wako, Osaka) followed by either ABC-DAB

processing, or Alexa 488 immunofluorescence. DAB-reacted sections were used for estimating densities of MC and length of processes using the NewCAST stereological software package (Visiopharm, Hørsholm). The same parameters were assessed on stacks of confocal images (acquired at high resolution in a Leica SP5 confocal microscope). The images were analyzed off-line with the help of Corel Draw software. Results showed a remarkable coincidence of data with the two methods, except for a moderate higher yield of fluorescent images. Analysis of both types of sections by two examiners resulted in a better than 96% coincidence. In addition, we are currently examining whether infiltrating macrophages contribute to the increased reactive cell population in the deafferented Sp5C. We believe that this study will help tackle the challenge of understanding the biology of MG in reliable quantitative terms.

Disclosures: **N. García-Magro:** None. **P. Negredo:** None. **Y. Martin:** None. **C. Avendano:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.04/DP03/C76

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: B.11. Glial Mechanisms

Support: IARPA D16PC00004

Title: Interactions between microglia and neurons in V1 visual cortex using 3D serial section electron microscopy

Authors: *J. BUCHANAN[1], A. A. BLECKERT[1], A. L. BODOR[1], D. J. BUMBARGER[1], F. COLLMAN[1], C. SCHNEIDER-MIZELL[1], M. M. TAKENO[1], T. MACRINA[2], S. DORKENWALD[2], N. L. TURNER[2], W. SILVERSMITH[3], K. LEE[3], J. WU[3], S. POPOVYCH[3], R. LU[3], N. KEMNITZ[3], E. FROUDARAKIS[4], J. REIMER[4], A. S. TOLIAS[4], H. SEUNG[3], R. C. REID[1], N. M. DA COSTA[1];
[1]Neural Coding, Allen Inst. For Brain Sci., Seattle, WA; [3]Princeton Neurosci. Inst., [2]Princeton Univ., Princeton, NJ; [4]Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Microglia are known for their complex actions in the brain, including homeostasis, synaptic stripping and phagocytosis. A subset, known as satellite microglia, are closely opposed to their host neurons. To better understand interactions of satellite microglia, their hosts, and other neurons in their territory, we used high throughput serial section EM and 3D reconstruction of a 250x150x100 µm volume of mouse (P 36) visual cortex. We examined microglia contacts in the 3D environment containing 38 microglia and 180 neurons in layer 2/3. We focused on fully

segmented microglia, both AXIS (axon initial segmented associated) (Fig.1) and non-axis type, following branches and fine processes to their termination on neuronal somas.
Individual microglia contacted somas of a subset of neurons, both excitatory and inhibitory within their territory, up to 15-20 per cell at distances of 1 to 50 µm from host. Their ramifications varied from long thin or thick branches, to ruffled protrusions and flat disks. The soma contact sizes ranged from 1 µm to 20 µm. Some processes exhibited complex hand or claw like formations, which appeared to be grabbing fine axons close to the soma. The territories of individual microglia ranged from 80 µm to 120 µm. The contacts with neuronal somas were not strictly nearest neighbor, but a subset of neurons inside the territory.
Within processes of individual microglia, there was evidence of phagocytic activity, supported by existence of small vacuoles (250 nm) and complex phagolysosomes (500 nm).
There were remnants of 50 nm synaptic vesicles inside the phagolysosomes, which appeared encapsulated within the cytoplasmic matrix of the process. Other axons looked partially engulfed within processes, but not encapsulated, reflecting trogocytosis rather than phagocytosis. These interactions may reflect fine scale refinement and homeostasis rather than large scale synaptic stripping and remodeling as occurs during development.

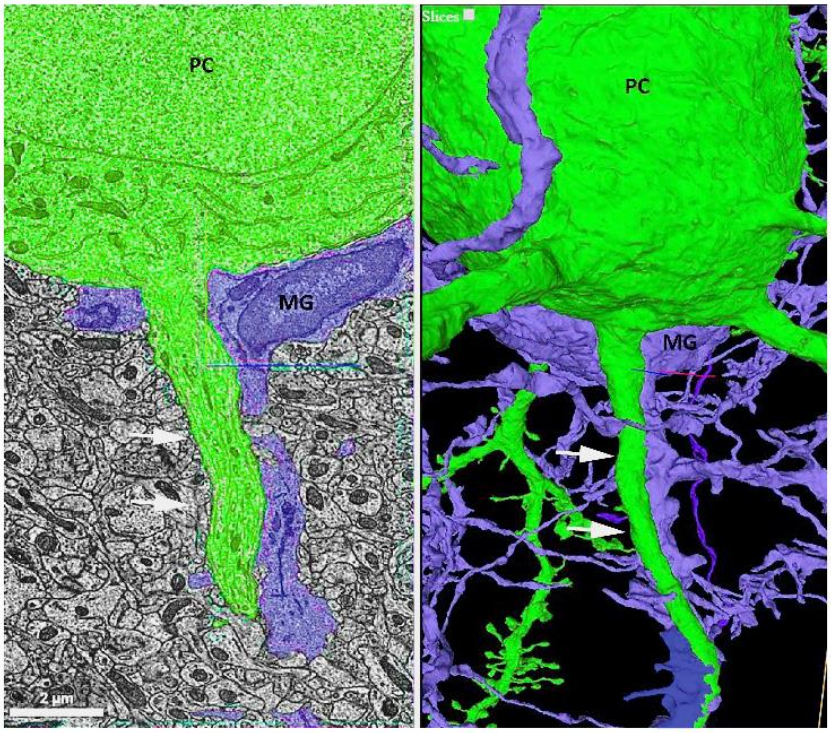

Figure 1. Major processes of satellite microglia (MG) contact axon initial segment (arrows) of host pyramidal cell neuron (PC). Scale bar 2 µm

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.05/C77

Topic: B.11. Glial Mechanisms

Support: JSPS Grant 18J20536

Title: The atypical cadherin Fat3 is necessary for morphological remodeling in postnatal microglia

Authors: ***T. OKAJIMA**[1], I. KO[2], B. SATO[1], T. CHIBA[1], F. TSURUTA[1];
[1]Grad. Sch. of Life and Envrn. Sci., [2]The Sch. of Life and Envrn. Sci., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Microglia, the resident immune cells in the central nervous systems (CNS), are necessary for the normal development and functions of the healthy brain. It has been shown that the gene expression profile continuously changes from embryonic stages to adulthood, and this variation is closely related to their morphology and functions. Intriguingly, the single cell transcriptome analysis has revealed that microglial heterogeneity peaks during development. Although the morphological changes mediated by gene expression is a key process for the microglial maturation, the mechanisms leading the transition to a mature phenotype are still poorly understood. Here, we reported that one of the atypical cadherin family, Fat3 is a novel candidate that support for the microglial maturation. We found that microglia cell line BV-2 exhibit dynamically extending their protrusions under high nutrient medium condition (HNM). In addition, we observed that the number of BV2 morphological shapes with protrusions are increased compared to normal medium condition. Using DNA microarray analysis, we found that expression of Fat3 is upregulated by culturing BV-2 under HNM condition. Knockdown of Fat3 decreased the microglial protrusions, demonstrating that Fat3 is necessary for inhibiting the retraction of these processes. We also found that Fat3 deficiency perturbed the coordination of microglial maturation through the changes of gene expressions such as CD68 and P2Y12, suggesting that Fat3 is a key factor that controls microglial heterogeneity. Our finding provides evidence that Fat3 expression controls microglial morphogenesis during the developmental stages.

Disclosures: **T. Okajima:** None. **I. Ko:** None. **B. Sato:** None. **T. Chiba:** None. **F. Tsuruta:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.06/C78

Topic: B.11. Glial Mechanisms

Support: NIH R01 AA027111 (AKM)
NSF grant 1557971 (AKM)

Title: The role of PI3Kg signaling in microglial dynamics and experience-dependent synaptic plasticity

Authors: *B. S. WHITELAW[1], A. K. MAJEWSKA[2];
[1]Univ. of Rochester, Rochester, NY; [2]Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Microglia are dynamic cells that interact extensively with neurons and glia during development, which allows them to regulate neurogenesis, refine neuronal networks, and influence synaptic plasticity. The same properties that allow microglia to shape the development of the CNS may also lead to neurological disease if not properly regulated. The extracellular signals that mediate microglial dynamics and interactions with neurons are not well understood. Signaling through extracellular nucleotides has emerged as a key mechanism by which microglia sense and interact with their external environment. Specifically, the microglial P2Y12 receptor is crucial for microglial responsiveness to extracellular adenosine tri-phosphate (ATP) and mediates numerous microglial functions, including ATP-dependent chemotaxis, microglia-neuron interactions, and experience-dependent synaptic plasticity. However, little is known about the downstream signaling effectors that mediate these diverse actions of P2Y12. Phosphoinositide-3-kinase gamma (PI3Kg), a lipid kinase activated downstream of Gi-coupled GPCRs such as P2Y12, could translate localized extracellular ATP signals into directed microglial action and serve as a broad effector of P2Y12-dependent functions. Here, we show that PI3Kg mediates the microglial response to laser-induced focal injury in acute slices, which depends on actin polymerization. We are currently investigating other partners in this chemotactic signaling cascade and determining the role of PI3Kg in microglial dynamics and synaptic plasticity *in vivo*.

Disclosures: **B.S. Whitelaw:** None. **A.K. Majewska:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.07/C79

Topic: B.11. Glial Mechanisms

Support: NIH Grant 1F99NS108486-01

Title: Newly-born microglial motility and surveillance *in vivo*

Authors: *J. B. ATLAS[1], M. S. MENDES[1], M. MCCALL[2], A. K. MAJEWSKA[1]; [1]Neurosci., Univ. of Rochester Med. Ctr., Rochester, NY; [2]Biostatistics, Univ. of Rochester, Rochester, NY

Abstract: Microglia support the central nervous system (CNS) through their primary role as rapid responders to injury and disease, as well as contributing to neurodevelopment and synaptic plasticity. Microglia maintain these roles and their relative presence in the CNS through a process of self-renewal. Nevertheless, this process of self-renewal and the subsequent maturation of microglia in adulthood remain poorly understood. To investigate these processes, we implemented a pharmacological approach of microglial depletion, enabling us to study the development of these cells as they repopulate the adult mouse brain. Accordingly, PLX5622 was administered in chow to $Cx3Cr1^{GFP/+}$ heterozygous mice starting on postnatal day 60 (P60). PLX5622 inhibits the colony-stimulating factor-1 receptor (CSF-1R), essential for microglial survival and repopulation, effectively eliminating the vast majority of microglia. This approach has been previously shown to yield a robust depletion of microglia in the adult visual cortex, after which microglia rapidly repopulate. In order to study microglial dynamics during maturation, time-lapse 2-photon imaging was conducted in mice via a chronic cranial window during depletion and repopulation. We observed that newly-born microglia rapidly acquire mature characteristics, particularly motility and surveillance, following the cessation of depletion treatment. Further, we observed that maturing microglia exhibit a long-term dysregulation of motility during depletion as they each survey their newly established microenvironment in the brain. These changes in microglial properties are not due to the presence of inflammatory signaling resulting from microglial depletion, as analysis of various cytokine levels as well as astrocytic morphology showed no differences between mice receiving the PLX5622 diet and controls. These findings demonstrate that newly-born microglia quickly resume a dynamic role as they repopulate their environment. Moreover, newly-born microglia may assume a hyper-vigilant state, potentially indicating a distinct level of responsiveness in anticipation of subsequent signs of injury or disease in the brain.

Disclosures: J.B. Atlas: None. **M.S. Mendes:** None. **A.K. Majewska:** None. **M. McCall:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.08/C80

Topic: B.11. Glial Mechanisms

Support: NIH Grant R01MH106553

Title: Intra-hippocampal depletion of microglia as a tool to examine the role of microglia in the ontogeny of learning and learning deficits produced by immune challenge

Authors: *M. B. BIELICKI, N. A. HAAS, J. M. SCHWARZ;
Psychological and Brain Sci., Univ. of Delaware, Newark, DE

Abstract: Early-life immune activation has been linked to male-biased developmental disorders, many of which are associated with learning deficits such as Autism, ADHD, and Schizophrenia. Microglia, the immune cells of the brain, are thought to be involved in the formation of hippocampal circuits important for learning during a critical juvenile period of development. We have found that immune activation with lipopolysaccharide (LPS), on postnatal day (P) 21 in rats, produces hippocampal-dependent learning deficits on P24 in the Context Pre-exposure Facilitation Effect (CPFE) fear-conditioning paradigm. We are currently examining the role of microglia in this learning deficit by selectively depleting microglia in the dorsal hippocampus (dHP) during this unique period of hippocampal development. Clodronate is a drug that, when encapsulated in liposomes, is selectively ingested by and results in the death of phagocytic cells. We infused 3 microliters of liposome-encapsulated clodronate (LEC) into the dHP of male and female rats (Sprague-Dawley) at P16 to determine whether LEC selectively depletes microglia during the critical developmental window during which context learning emerges (P21-24). Immunohistochemical (IHC) staining and RT-PCR were utilized to examine changes in microglia density and gene expression in dHP. We found that LEC decreased the density of microglia and reduced cytokine expression in dHP during this important juvenile period for learning. We then examined how microglial depletion in dHP affected cytokine expression produced by LPS immune activation on P21. Our goal is to determine whether depletion of microglia prevents or potentiates learning deficits in the CPFE paradigm, either alone or following LPS challenge. These experiments will elucidate the role of microglia during a juvenile immune activation and in the development of hippocampal circuits that control learning.

Disclosures: M.B. Bielicki: None. **N.A. Haas:** None. **J.M. Schwarz:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.09/C81

Topic: B.11. Glial Mechanisms

Support: ECR/2016/001169

Title: Transcriptional regulation of microglia development and function

Authors: *V. SAHASRABUDDHE, P. KA, H. GHOSH;
NCBS, Bengaluru, India

Abstract: Microglia are the resident macrophages of the central nervous system. They are unique in CNS with regards to their developmental origin and self-renewal capacity. During the course of development, microglia undergo a continual transformation from an immature amoeboid morphology and a phagocytic, proliferative functional state to a mature ramified state with surveillance and synaptic remodeling as their main functions. These functional transformations are also reflected in their distinct, stage-specific transcriptomes. Understanding molecular mechanisms and transcriptional networks that regulate distinct microglial developmental states and enable switching from one functional state to another, is an active area of research.
To this end, we are exploring the role of a basic-helix-loop-helix transcription factor in microglia. Given its known disease relevance and continual expression in mammalian brain, it is important to understand its function in homeostasis. So far, expression and potential roles of this transcription factor remain relatively unexplored, particularly in glial cells. Using inducible CreER-LoxP system for cell- and time- specific deletion of our gene-of-interest in a mouse model, we have identified the role of a novel gene in microglia development. Our preliminary phenotype characterization with microscopy and Fluorescence Activated Cell Sorting (FACS) suggests its functions in maintaining homeostatic microglial frequency and surface profile. We are currently conducting differential gene expression analysis to get mechanistic insights.
Our work could provide new insights about regulation of microglial transcriptional and functional states.

Disclosures: V. Sahasrabuddhe: None. **P. Ka:** None. **H. Ghosh:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

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Program #/Poster #: 469.10/C82

Topic: B.11. Glial Mechanisms

Support: Japan Society for the Promotion of Science - KAKENHI (C)

Title: The effects of anti-Alzheimer's drug donepezil on rodent microglial functions

Authors: *Y. MIZOGUCHI, A. MONJI;
Dept. Psychiatry, Fac. Medicine, Saga Univ., Saga, Japan

Abstract: Microglia are resident innate immune cells which release many factors including proinflammatory cytokines or nitric oxide (NO) when they are activated in response to immunological stimuli. Pathophysiology of Alzheimer's disease (AD) is related to the inflammatory responses mediated by microglia. Intracellular Ca^{2+} signaling is important for microglial functions such as release of NO and cytokines. In addition, alteration of intracellular Ca^{2+} signaling underlies the pathophysiology of AD. We had reported that pretreatment with donepezil, an acetylcholinesterase inhibitor, suppressed the TNFα-induced sustained intracellular Ca^{2+} elevation in rodent microglial cells. Using DAF-2 imaging, we also found that pretreatment with donepezil suppressed the production of NO induced by TNFα treatment and the PI3K pathway could be important for the donepezil-induced suppression of NO production in rodent microglial cells. The phagocytosis assay showed that pretreatment with donepezil promoted phagocytic activity of rodent microglial cells through the PI3K pathway. We also tested the effects of donepezil on cellular surface expression of some key proteins such as TREM2 which are important for phagocytosis. These suggest that donepezil could directly modulate the microglial function including phagocytic activity.

Disclosures: Y. Mizoguchi: None. **A. Monji:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.11/C83

Topic: B.11. Glial Mechanisms

Support: Conacyt 255317

Title: Epigenetic modulation of microglia modulates the proinflammatory cytokines expression *in vitro*

Authors: *G. CRUZ[1], L. MONTALVO MARTINEZ[3], L. FUENTES-MERA[4], A. CAMACHO[2];
[1]Univ. Autónoma De Nuevo León, Monterrey, Mexico; [2]Univ. Autónoma De Nuevo León, Nuevo León, Mexico; [3]Biochem. and Mol. Med., Autonomous Univ. of Nuevo León, Ciudad Santa Catarina, Mexico; [4]Univ. Autonoma de Nuevo Leon, Monterrey, Mexico

Abstract: Obesity integrates a low-grade chronic inflammation of peripheral and central organs. It has been shown that toll like receptor - 4 (TLR4) directly modulates inflammation, neurotoxicity and selective behaviors. Microglia in brain efficiently integrates external stimulus contributing to inflammatory responses to disease or injury. Of importance, inflammation might be closely programmed by epigenetic mechanisms during exposure to caloric diets, a pathological mechanism known as "immune priming". Here we tested if pharmacologic epigenetic modulation coordinates pro inflammatory cytokines expression following metabolic stimuli in a microglia *in vitro* model. Microglia cells (SIMA9) were pretreated with inhibitors (5-Azatidine (AZA75nM)) or promoters (S-Adenosylmethionine (SAM 250µM)) of methylation or acetylation promoters (Suberanilohydroxamic acid 500nM) for 24 hours, following by with 100mM palmitic acid or 500ng lipopolysaccharide (LPS) stimulation for 6 hours. Proinflammatory gene expression was analyzed by real time PCR. We found that LPS stimulation promotes IL-6 and IL-1β expression which is positively favored by a methylation or acetylation mechanism induced by SAM or AZA treatment, respectively. By contrast, a decrease in the TNFα expression was found following LPS incubation under methylation or hypomethylation scenarios induced by SAM or AZA, respectively. Of note, microglia hypomethylation induced by the AZA treatment for 6 hours increases the expression of IL-6 following palmitic acid stimulation. Also, palmitic acid increases the IL-1β and IL-1α cytokines following SAHA and AZA, respectively. Finally, TNFα expression decreases during hypo or high methylation induced by SAM or AZA + palmitic acid, whereas acetylation induced by SAHA favoring it at 24 hours. In conclusion, gene expression of IL-6 efficiently responds to changes in methylation, while acetylation positively modulates IL-1β expression, both during LPS and palmitic acid stimulation.

Disclosures: G. Cruz: None. **L. Montalvo Martinez:** None. **L. Fuentes-Mera:** None. **A. Camacho:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.12/C84

Topic: B.11. Glial Mechanisms

Support: Creighton Health Science Strategic Initiative Award

Title: A long non-coding RNA promotes anti-inflammatory microglial polarization and anti-viral defense

Authors: N. W. MATHY[1], P. J. MARTA[2], A. P. KOCHVAR[3], K. M. DRESCHER[1], *A. SHIBATA[3];
[1]Med. Microbiology and Immunol., [2]Sch. of Med., [3]Biol., Creighton Univ., Omaha, NE

Abstract: Upon activation, microglia become polarized towards either the classical M1 pro-inflammatory or M2 anti-inflammatory phenotypes. Increased understanding of the regulatory factors controlling microglial polarization may be critical to modulating inflammation in the CNS. Long non-coding RNAs (lncRNAs) are transcripts that lack protein coding potential and have been shown to regulate gene expression. LncRNAs are likely involved in the regulation of microglial phenotypes and inflammatory processes in the CNS. To identify lncRNAs involved in neuroinflammation, we used microarray analysis. We identified several lncRNAs of interest. LncRNA-25B is significantly upregulated in response to LPS in a microglial cell line compared to IL-4 and unstimulated cells. Validation of the microarray by RT-qPCR showed a 20-fold induction after 6h of LPS stimulation compared to control. Overexpression of lncRNA-25B in microglial cells for 24h significantly reduced levels of M1 markers iNos by 0.5 fold and IL-1β by 0.4 fold and significantly increased M2 markers such as Arginase1 by 4.0 fold as compared to empty vector control (n=3). Knockdown of lncRNA-25B reciprocally decreased levels of Arginase1 by 0.4 fold compared to scrambled siRNA (n=3). To explore the potential *in vivo* significance of lncRNA-25B in neuroinflammation, we utilized a well-established murine model of multiple sclerosis using Theiler's Murine Encephalomyelitis Virus. Analysis of RNA collected from whole brain extracts showed a significant increase in lncRNA-25B (3.1 fold, n=3) in infected animals compared to controls. *In vitro* data demonstrated a significant induction of lncRNA-25B (2.75 fold) after 24h infection of the microglial cell line with 0.1 MOI of TMEV. UV-inactivated virus did not induce lncRNA-25B. Further, overexpression of lncRNA-25B reduced viral burden in microglial cells by 81% compared to the empty vector control, while knockdown of lncRNA-25B significantly increased the viral burden by 2.73 fold compared to a scrambled siRNA. Irf7, a master regulatory of the anti-viral type 1 interferon response, participates in the polarization of microglia. Interestingly, overexpression of lncRNA-25B alone significantly induced expression of Irf7 compared to empty vector control (2.18 fold), while

knockdown of lncRNA-25B significantly decreased Irf7 mRNA levels (0.56 fold). Future experiments will probe the molecular mechanism of Irf7 regulation by lncRNA-25B.

Disclosures: **N.W. Mathy:** None. **P.J. Marta:** None. **A.P. Kochvar:** None. **K.M. Drescher:** None. **A. Shibata:** None.

Poster

469. Microglial Functions in Brain Development and Homeostasis

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Topic: B.11. Glial Mechanisms

Support: NIH F32-105363-02
NIH R01-102272-02

Title: Microglia: Local mRNA translation and synaptic homeostasis

Authors: ***M. VASEK**[1], Y. LIU[1], J. DEAJON-JACKSON[1], J. D. DOUGHERTY[2]; [1]Genet., Washington Univ., Saint Louis, MO; [2]Genet. and Psychiatry, Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: The processes of a single adult microglia make about 300 contacts per hour with neighboring synapses, glia, and vascular endfeet in a healthy brain. During these brief contacts, microglia are receiving signals from neuronal and glial contacts and responding to them through the release of trophic factors and cytokines or by phagocytizing debris, apoptotic cells, and inappropriate synapses. We hypothesize that microglia, like neurons and astrocytes, employ selective mRNA transport and local protein synthesis within their distal processes in order to orchestrate simultaneous and heterogenous responses at each of their many distal loci. Here we show, *in vivo*, that distal murine microglial processes contain mRNAs, ribosomes, and *de novo* protein synthesis through *in situ* hybridization, electron-microscopy, and puromycylation studies, respectively. Additionally, acute blockade of protein synthesis impairs microglial phagocytosis of debris in an *ex vivo* slice model, suggesting that protein synthesis is necessary for this process. We have also identified a list of *in vivo* microglial perisynaptic-enriched mRNAs through translating ribosome affinity purification followed by RNA sequencing on synaptoneurosome fractions of cortical microglia. Microglial mRNA transcripts localized to perisynaptic sites include genes known to modulate synapses, play roles in microglia-neuron signaling, or are known to be dysregulated during CNS inflammation or neurodegenerative disease, including Cathepsin S, Siglec H, classical complement component proteins, and Triggering receptor expressed on myeloid cells 2 (TREM2). Taken together, these data suggest that microglia contain a distinct distal perisynaptic translatome where proteins involved in synaptic remodeling and homeostasis can be locally translated.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.14/C86

Topic: B.11. Glial Mechanisms

Support: FAPESP 16/22793
FAPESP 13/21728-2
CNPq 304126/2015-2.

Title: The effects of air pollution on microglia cell of the olfactory bulb

Authors: ***N. V. DOS SANTOS**[1], C. R. ARAUJO[1], L. T. JUSTO[1], S. M. O. SHINJO[2], C. D. S. DE ANDRÉ[3], P. H. SALDIVA[1], S. K. N. MARIE[2];
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Abstract: The complexity of the urban environment makes it very difficult to establish the effects of pollutants on the central nervous system (CNS) of humans. Studies have reported that neurological dysfunctions such dementia may also be associated to air pollution exposure, and have shown that animals, child, and adults living in polluted areas exhibit neuroinflammation and the breakdown of the blood-brain barrier. The airborne fine particulate matter (PM2.5) can enter in the olfactory epithelium, to be transported to the olfactory bulb, and to even reach the olfactory cortex and other brain regions. Recent findings indicate that microglia can detect and respond to inhaled pollutants, indicate that cell may be critical actors responsible for cellular damage caused by pollutants, causing damage, local inflammation and stress responses. While the air pollution effects are not yet understood, suggested causes include microglia activation and neuroinflamation. To investigate this hypothesis fresh samples of olfactory bulb were obtained from 14 individuals from Post Mortem Verification Service of São Paulo city (SVOC) with inclusion criteria: age equal or greater than 18 years, be living in the MASP for at least 3 months, have one close relative to provide reliable and complete information during the interview (previous health conditions, residential address, sociodemographic details, life habits, smoking status, occupation, time of residence in the MASP and time spent commuting) and present no macroscopic alterations of the lungs, brain and in olfactory epithelium. For the anthracosis index it was measured in the pleural surface of the lungs during the autopsy. The pleura surface was photographed and using this images to determine the fraction area of anthracosis. The olfactory bulb were fixed with 4% paraformaldehyde and processed for immunohistochemical assessments. 5 µm-thick paraffin sections were labeled with anti-IBA1 (anti ionized calcium

binding adaptor molecule 1) antibody, as a marker of microglia. Our results show an increased of microglia cell deposition on one side of the olfactory bulb, side that is in contact with the ethmoid bone. We also found a negative correlation ($r = -0.565$, $p = 0.035$) between anthracosis and microglia rate, the trend was maintain in regression models with controlling variables: age, socio-economic index, smoke and gender ($r2=73\%$). This reveals that the microglia role in the neuroinflamation by air pollution is much more complex than previously thought.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

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Program #/Poster #: 469.15/C87

Topic: B.11. Glial Mechanisms

Support: NIGMS P20 COBRE Award (5P20GM109025)

Title: Evaluation of GPCR function on glia in the regulation of inflammatory signaling

Authors: *N. L. KOLCH, A. M. SALAZAR, S. M. HERNANDEZ, M. J. KIMMICH, J. W. KINNEY;
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Abstract: Inflammation in the CNS is a necessary response to harmful toxins, brain injury, and other various acute insults. It is not only very critical for the prevention of further damage, but also to promote additional protection to the CNS. Sustained inflammatory signaling (neuroinflammation) in the CNS has been demonstrated to occur in several neurodegenerative disorders, in particular Alzheimer's disease (AD), and promote pathological features of the disease. The activation of microglia serves as initial inflammation response that results in the production of pro-inflammatory cytokines and phagocytosis. However, the chronic activation of microglia imposes negative effects such as enhanced microglial senescence, dysfunctional phagocytosis, and cell death, and further, on several signaling mechanisms in the brain. Given the deleterious effects of neuroinflammation, understanding the mechanisms that relates to the reduction of pro-inflammatory signaling and/or promoting anti-inflammatory signaling is

needed.
Microglia express a number of G-protein coupled receptors (GPCR) that have been implicated in mediating its activation state. In addition, several compounds that bind to these GPCRs have been reported to impact neuroinflammation and other AD-related deficits. However, further description of the underlying mechanisms of these impacts are still needed. In our study, we have investigated the impacts of GPCR ligands on pro- and anti-inflammatory cytokine levels prior to and after the induction of immune response in BV2 cells and glial cultures. We have employed several techniques such as immunoblotting, immunohistochemistry, and Real-Time PCR, to analyze the expression levels of GPCR and cytokines. Our data indicate that activation of specific GPCRs directly impacts expression levels of both pro- and anti-inflammatory signaling cytokines, which can shed light on some important interactions between these signaling molecules.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

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Program #/Poster #: 469.16/C88

Topic: B.11. Glial Mechanisms

Support: NIH Grant RO1 MH52716
NIH Grant R01 DA039062
NIH Grant R01 MH091424
NOH Grant P01HD085928

Title: Characterization of a CRISPR-generated rat model containing eGFP-Iba1 for study of microglia

Authors: *M. M. MCCARTHY[1], J. W. VANRYZIN[1], K. E. KIGHT[3], E. L. REINL[1], A. E. MARQUARDT[2], S. E. ARAMBULA[1], S. E. ASHTON[2], K. T. DAVIS[1], L. A. PICKETT[2], A. HOLLEY[4];
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Abstract: Microglia are the innate immune cells of the brain and display a unique profile of motility and mobility, the study of which can be greatly enhanced by endogenous expression of a fluorescent reporter gene. Iba1 (also called Aif1, Gene ID: 29427) is expressed by all microglia in the brain, some peripheral macrophages and in the testis. The generation of a Sprague-Dawley

rat strain with eGFP expression driven by the Iba1 promoter generated by CRISPR-Cas9 technology was contracted to Applied Stem Cell (Milpitas, CA) by the University of Maryland School of Medicine. Two male and four female homozygous founders were provided and used to generate a colony of transgenics we call the MicGlo Rat. Breeding reveals Mendalian inheritance of the transgene with homozygotes being fully viable but expression of eGFP is variable, the source of which is under investigation. Flow sorting of homogenized brain tissue reliably detects eGFP in Iba1 expressing cells and qPCR of FAC sorted eGFP cells confirmed enrichment of microglia specific genes and a lack of neural and astrocytic genes. Immunohistochemical detection of eGFP and Iba1 in brain tissue sections reveals complete overlap with no extraneous eGFP. Preparation of ex vivo sections indicates eGFP expression is suitable for live-cell imaging in some, but not all, cases. Ongoing characterization of the MicGlo Rat will be reported.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.17/C89

Topic: B.11. Glial Mechanisms

Support: NIMH-R00MH102351
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T32A1095212-07
Brain & Behavior Research Foundation
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: The fractalkine receptor regulates microglia-vascular interactions in the developing brain

Authors: *E. MONDO[1], A. G. KAUTZMAN[1], S. C. BECKER[1], S. L. LIRA[2], D. P. SCHAFER[1];
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Abstract: Microglia, a resident central nervous system (CNS) macrophage, are born in the yolk sac and take up residence in the CNS embryonically. Once in the brain parenchyma, the precise mechanism regulating the timing of microglial localization to the appropriate brain region remains unknown. Here, we show that microglia are highly associated with vasculature during early postnatal development, a time of active microglial colonization, and these vascular-associated microglia are proliferative and phagocytic. Further, we identify that these microglia-

vascular interactions are dependent on the fractalkine receptor (CX3CR1), but not the canonical CX3CR1 ligand, fractalkine (CX3CL1). Finally, previous work has shown that microglial recruitment to synapses in layer IV of the barrel cortex is critical for the timing of synapse maturation via CX3CR1. We demonstrate that microglia are highly associated with the vasculature during the time in which they are recruited to layer IV synapses of the barrel cortex, and the timing of these microglia-vascular interactions is delayed in CX3CR1 deficient mice. These data provide a new role for CX3CR1 in regulating microglia-vascular interactions in the developing brain, independent of CX3CL1. We further identify an underlying mechanism by which CX3CR1 may regulate the timing of microglial to synapses and subsequent synapse maturation.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

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Topic: B.11. Glial Mechanisms

Support: NIH TL1 TR001454
NIMH R01 MH113743
NARSAD 125458

Title: Microglial derived innate immune mechanisms governing neural excitability

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Abstract: During development and continued through adulthood, elaborate mechanisms are used to establish and maintain the appropriate amount and balance of excitation & inhibition (E/I balance). The clinical relevance is exemplified in neuropsychiatric disorders, such as autism spectrum disorders (ASDs), where defects in E/I balance are believed to underlie some of the core clinical features including repetitive behaviors, impaired sociability and increased propensity for seizures. Another emerging feature in ASD are increased inflammatory microglia, a resident macrophage of the central nervous system. Here, we are exploring whether changes in microglial inflammatory state affect E/I balance relevant to neuropsychiatric disease. We show that mice harboring null mutations in interferon regulatory factor 8 ($IRF8^{-/-}$), a transcription factor necessary for modulating inflammatory signaling in microglia, have significantly increased cortical and hippocampal c-Fos, an activity-dependent immediate early gene, in the absence of significant changes in synapse density. In addition, upon administration of

chemoconvulsants there is a profound increase in seizure severity and excitotoxicity. Because IRF8 is highly enriched in microglia in the context of the brain, these data suggest that microglia-derived inflammatory, neuroactive cytokines could be critical to regulate neuronal excitability and E/I balance through synaptic pruning-independent mechanisms. We are now identifying and determining how IRF8-dependent, microglia-derived factors modulate neural excitability, which could have important implications for ASD.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: B.11. Glial Mechanisms

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Charles H. Hood Foundation
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Worcester Foundation
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation

Title: Sensory lesioning induces microglial synapse elimination via ADAM10 and fractalkine signaling

Authors: *G. GUNNER[1], L. CHEADLE[3], K. M. JOHNSON[5], P. AYATA[6], A. BADIMON[8], E. MONDO[1], A. M. NAGY[3], L. LIU[9], S. M. BEMILLER[10], K.-W. KIM[11], S. A. LIRA[7], B. T. LAMB[12], A. R. TAPPER[2], R. M. RANSOHOFF[13], M. E. GREENBERG[4], A. SCHAEFER[14], D. P. SCHAFER[1];
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Abstract: Microglia, resident central nervous system macrophages, dynamically survey their neuronal environment and prune away less active synaptic connections. Recent work has

implicated the classical complement cascade in regulating microglia-mediated synapse engulfment and elimination in development and neurodegenerative disease. Here, we identify a complement receptor 3-independent mechanism by which microglia engulf and eliminate synapses in the somatosensory cortex following peripheral sensory deprivation. We find that the microglial chemokine receptor, CX3CR1, is necessary for whisker deprivation-induced microglial engulfment and elimination of structural and functional thalamocortical inputs. Interestingly, microglial recruitment to synapses following whisker removal was relatively unaffected in *Cx3cr1*$^{-/-}$ mice. We then show that the CX3CR1 ligand fractalkine (CX3CL1) is enriched in neurons and phenocopies synapse elimination defects in CX3CR1-deficient mice. To gain more insight into how this signaling is regulated, we performed single-cell RNAseq. These data reveal that, while *Cx3cl1* expression is unchanged, *Adam10*, a gene encoding the metalloprotease known to post-translationally cleave CX3CL1 into a soluble chemokine, is upregulated in the deprived cortex after sensory lesioning. Further, pharmacological inhibition of ADAM10 inhibits microglia-mediated removal of TC-inputs in the deprived cortex. These data support a mechanism by which cleavage of membrane-bound CX3CL1 by ADAM10 is necessary for neuronal signaling to microglia via CX3CR1 to induce synaptic engulfment and elimination following sensory deprivation. Together, we demonstrate that microglia coopt diverse neural-immune signaling mechanisms in different contexts to modify synaptic connectivity and provide new insight into how CX3CR1-CX3CL1 regulates microglial function at synapses in an activity-dependent manner.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.20/C92

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

Support: University of Washington Mary Gates Endowment Undergraduate Research Scholarship
Paul G. Allen Family Foundation #11856

Title: Microglia involvement in the development of the human fetal retina

Authors: *K. M. ESCHENBACHER, T. REH, A. SRIDHAR, L. TODD, A. HOSHINO; Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Studies in model organisms have shown that microglia have important roles in neural development, particularly in formation of synaptic circuitry. We are interested in understanding what aspects of development these cells regulate in the human retina. The timing of microglial migration into the central nervous system (CNS) has been described for several species, but it is currently not known when these cells enter the human retina. One previous study found these cells were present in the retina as early as fetal day (FD) 70. To determine when microglia enter the human retina during development and to better characterize their distribution, we analyzed developing human fetal retina for the presence of microglia from FD45 to FD163 using immunofluorescence and single-cell RNAseq analysis. We found that Iba1-positive microglia are present as early as FD45, and are primarily concentrated in the ganglion cell layer (GCL) and have morphologies typical of microglia in other regions of the CNS. Iba1+ cells are also present in the vitreous and extra-retinal tissues, such as the choroid at this age. Over time, Iba1+ microglia continue to be primarily located in the GCL, with some cells also present in the inner plexiform layer (IPL) and are distributed across the retina. We also used single cell RNAseq to track changes in microglial gene expression across several ages of development and these confirmed their presence prior to FD70. Our results show that microglia are present in the human retina earlier than previously described and may have roles in development at these stages. Finally, we compared the microglia numbers across dissociated cell and 3D fetal retina culture systems, and our results show that microglia numbers are increased in dissociated cultures. Overall, our results highlight the use of the fetal retina *in vitro* system to investigate the roles of microglia in neural development.

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Poster

469. Microglial Functions in Brain Development and Homeostasis

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 469.21/D1

Topic: B.11. Glial Mechanisms

Support: Research Fellowship for Young Scientists, Japan Society for the Promotion of Science

Title: Micronuclei released from neurons regulate the microglial activity during brain development

Authors: *S. YANO[1], H. KUBOTANI[2], B. SATO[1], T. CHIBA[1], F. TSURUTA[1];
[1]Grad. Sch. of Life and Envrn. Sci., [2]The Collage of Biol. Sci., Univ. of Tsukuba, Tsukuba, Japan

Abstract: Microglia critically contribute to the conditioning brain environment through phagocytosing cell debris or damaged neurons. In response to the secreting factor from the damaged neurons, microglia transform into active phagocytic forms, migrate, and accumulate around the target cells. When microglia sense exposed eat-me signals, they recognize and eliminate the target cells, contributing to the maintenance of the brain environment. However, the mechanism by which microglia recognize and remove the damaged neurons during development has not been fully understood. Here, we proposed that the micronuclei are secreted from neurons during the developmental stage, followed by regulating microglia activity. Micronuclei are cytosolic chromatin structures that are compartmentalized by a nuclear envelope. We found that micronuclei emerge in migrating neurons and are cleared by the autophagic pathway. Accumulated micronuclei are secreted to the extracellular region when the autophagic pathway is vulnerable in neurons. Besides, released micronuclei from neurons are taken up by the microglia *in vitro*. Using the neuron-specific nuclear membrane labeling mouse, we found that some micronuclei in microglia might originate from the neuronal micronuclei *in vivo*. Moreover, these microglia exhibit amoeboid shape and have thicker primary branches with larger cell bodies. Taken together, these data provide evidence that micronucleus is a novel factor involved in the neuron-microglia communications to maintain the brain environment, and suggest a possibility that they act as a novel microglia-activating factor that underlies the development of the brain.

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Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.01/D2

Topic: C.01. Brain Wellness and Aging

Title: Vascular and neurogenic rejuvenation in aging mice by modulation of ASM

Authors: *J.-S. BAE[1], S. HAN[1], J. LEE[1], K. PARK[1], I. JUNG[1], H.-J. KIM[3], **H. JIN**[2]; [1]Dept. of Physiology, Sch. of Med., [2]Col. of Vet. Med., Kyungpook Natl. Univ., Daegu, Korea, Republic of; [3]Dept. of Neurology, Col. of Med., Hanyang Univ., Seoul, Korea, Republic of

Abstract: Although many reports have revealed dysfunction of endothelial cells in aging, resulting in blood-brain barrier (BBB) breakdown, the underlying mechanism or mechanisms remain to be explored. Here, we find that acid sphingomyelinase (ASM) is a critical factor for regulating brain endothelial barrier integrity. ASM is increased in brain endothelium and/or plasma of aged humans and aged mice, leading to BBB disruption by increasing caveolae-mediated transcytosis. Genetic inhibition and endothelial-specific knockdown of ASM in mice

ameliorated BBB breakdown and neurocognitive impairment during aging. Using primary mouse brain endothelial cells, we found that ASM regulated the caveolae-cytoskeleton interaction through protein phosphatase 1-mediated ezrin/radixin/moesin (ERM) dephosphorylation and apoptosis. Moreover, mice with conditional ASM overexpression in brain endothelium accelerated significant BBB impairment and neurodegenerative change. Overall, these results reveal a novel role for ASM in the control of neurovascular function in aging, suggesting that ASM may represent a new therapeutic target for anti-aging.

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Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

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Program #/Poster #: 470.02/D3

Topic: C.01. Brain Wellness and Aging

Support: XDB32060200
XDB32070100
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18JC1410100

Title: Impaired dynamic of high frequency EEG in insomnia and major depression disorder

Authors: *J. J. JIANG, Sr, H.-C. CHANG, P.-Y. QIU;
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Abstract: Many psychiatric and neurodegenerative diseases including major depression disorder (MDD) are highly comorbid with a range of sleep disorders(1-4). Hyperarousal, which is mainly characterized as the increasing of the beta power density during NREM sleep, is consistent with the subjective feeling of insomnia patients(5-10). Insomnia monkey constructed by knocking out the circadian gene BMAL1(11) displayed Impaired dynamics of high frequency EEG (50-100Hz) which is not payed attention to by traditional sleep analysis. By calculating the relative entropy of the sleep/awake EEG, we found that the beta dynamic of homozygous monkeys is much more sensitive to the change of environment light exposure than that of the heterozygous and wild type ones. The dynamics of beta but not gamma oscillations can be partially rescued by melatonin application. Similar impairment was also found in primary insomnia patients and MDD patients. What's more, the dynamics of beta oscillation is negatively correlated with the HAM-D scores of the MDD patients. And the similar impairment may also exist in schizophrenia and bipolar disorder patients.Thus, we expanded the frequency range of sleep EEG

analysis to high gamma band. And the dynamics of high frequency oscillation of sleep EEG can be used as a stable and reliable marker of sleep quality.

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Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

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Program #/Poster #: 470.03/D4

Topic: C.01. Brain Wellness and Aging

Support: Internal funding grant for interdisciplinary research in Ben Gurion University of the Negev

Title: From a deep learning model back to the brain - Inferring morphological markers and their relation to aging

Authors: *G. LEVAKOV[1], G. ROSENTHAL[1], T. RIKLIN RAVIV[2], I. SHELEF[3], G. AVIDAN[4];
[1]Dept. of Cognitive and Brain Sci., [2]Dept. of Electrical and Computer Engin., [3]Dept. of Imaging, [4]Dept. of Psychology, Ben Gurion Univ. of the Negev, Beer Sheva, Israel

Abstract: Deep convolutional neural networks (CNN) enabled a major leap in image processing tasks including brain imaging analysis. In this work we utilized CNN for age prediction based on T1 MRI. Whereas CNN provides high predictive power, it is often difficult to identify the features that underlie a given prediction, hence these findings are regarded as 'black box' solutions that are difficult to interpret. Discovering which features, or brain structures, contribute most to the prediction of a given model have significant theoretical and translational value. Previous work examined methods to attribute pixel/voxel-wise contribution to the prediction in a single image, resulting in 'explanation maps' (EM) that were found noisy and unreliable. Here, we developed a novel inference framework for combining these maps across subjects, which allow us to achieve a more coherent, reliable measure of the contribution of different anatomical regions to the model's prediction. Our inference scheme was as follows: 1. Compute the derivative of each voxel in a given input volume with respect to the trained model's output. 2. Register different EM to subjects' native anatomical space and then to a common template to enable combining or comparing them 3. Average and threshold these maps to gain a population level EM. We demonstrate this method using CNNs ensemble trained on predicting subjects' age from anatomical T1 brain images of 10,176 healthy subjects, obtained from various open-source datasets. We focus on normal aging considering its widespread effects on brain structure and function. Evaluating the model on an untouched test (n = 588) resulted in MAE of 3.07 years and a correlation between the chronological and predicted age of r=0.98. Using the inference

method, revealed that cavities containing CSF had the highest contribution for age prediction in our model, in line with previous studies reporting a significant age-related volumetric increase. These were followed by subcortical GM, WM, and finally cortical GM. To validate our method, we showed that it substantially increases the replicability of the EM as a function of sample size. Moreover, benchmarking our results against a baseline of VBM studies revealed a significant overlap. Finally, we demonstrate that the model highlights brain regions that had the highest sensitivity to inter-subject volumetric variability. To conclude, we provide a framework for utilizing basic population statistics on a large collection of EM in the context of brain aging. This allows us to highlight specific brain regions exploited by the CNN model and thus provide an insight on the underlying neuroanatomical processes.

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Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

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Program #/Poster #: 470.04/D5

Topic: C.01. Brain Wellness and Aging

Support: USANA Health Sciences (BAB)
NIH RISE grant 5R25GM077634-04 (UNCP)

Title: American ginseng extract amplifies the autophagic-lysosomal protein clearance pathway and prevents synaptic decline in the hippocampal explant model of age-related protein accumulations stress

Authors: *M. FERNANDES DE ALMEIDA[1], M. C. PAIT[1], K. M. RENTSCHELER[1], K. L. G. FARIZATTO[1], C. J. NORTON[1], D. N. UPADHYAY[1,2], L. D. HOLMES[1,2], J. TIAN[3], M. FUHRMAN[3], *B. A. BAHR[1,2];
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Abstract: Brain aging causes gradual synapse loss, slowly influencing cognitive function and explaining why aging is a major risk factor for protein accumulation disorders including Alzheimer's disease (AD). Acceptance is growing for the ideas that exercise and specific foods help avoid poor cognitive aging, noting that a healthy diet is linked to a 40% lower risk for dementia (Sohn, *Nature* 2018 559:S18). Here, plant extracts were tested for their influences on the brain's autophagy-lysosomal pathway and related cathepsin enzymes involved in protein clearance. Particular focus was on cathepsin B (CatB) since it is increased by exercise, and the

CatB enhancement level correlated with improved memory in monkeys and humans (Moon et al. *Cell Metab*. 2016 24:332). Compounds that augment CatB activity were also found to reduce pathogenic proteins and improve synaptic integrity in three AD models (Butler et al. *PLoS ONE* 2011 6:e20501; Farizatto et al. *PLoS ONE* 2017 12:e0182895). Two plant extracts markedly increased the 30-kDa active form of CatB (CatB-30) when applied to hippocampal slice cultures for 3 days. American ginseng (P. quinquefolius) produced a 4-fold increase and the CatB modulation correlated with measures of the synaptic protein GluR1. Bacopa extract (B. monnieri) caused similar CatB-30 enhancement but without correlating with GluR1. Small increases in CatB-30 were produced by Panax ginseng and wild blueberry extracts, and all extracts tested were deemed safe in routine cell viability assays. In a model of age-related protein accumulation stress, American ginseng was the most effective for increasing the autophagy marker LC3-II, reducing protein ubiquitination, and protecting synaptic integrity in brain slices treated with the lysosomal inhibitor chloroquine. Chloroquine is well-known for producing age-related compromise of the autophagy-lysosomal pathway and the typical synaptic decline associated with such stress. These results indicate that select natural products can positively influence a protein clearance pathway in the brain to promote synaptic maintenance. The findings suggest that CatB positive modulation leads to enhanced synaptic health, providing a preventative strategy to preserve proteostasis and reduce the risk of age-related cognitive impairment.

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Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.05/D6

Topic: C.01. Brain Wellness and Aging

Title: Magnetic resonance diffusion tensor imaging reveals white matter degradation in aging mouse brain

Authors: *M. ZHU[1], C. AKIMANA[2], E. WANG[2], C. K. NG[1];
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Abstract: Introduction: Magnetic resonance diffusion tensor imaging (DTI) is a widely accepted tool to study microstructural changes of white matter (WM) based on diffusion properties of the WM regions [1]. Previously, several groups have reported age-related WM diffusion changes using various Alzheimer's Disease mouse models [2-4]. However, as of today, there is no DTI

study of WM diffusion in mice during normal aging process, especially those beyond 20 months old. Thus the objective of the current study was to assess progressive diffusion changes during aging in both hippocampal (gray matter) and corpus callosum (white matter) regions.
Methods: Four age groups of C57BL/6 male mice (4, 11, 18, and 27 months, n = 5 for each group) were scanned using a 9.4 T horizontal bore MRI system. A standard spin echo multi-slice (SEMS) imaging sequence was used for DTI acquisition. DTI data were converted and analyzed by DTI quantification software, DTIStudio. Four DTI parameter maps were calculated: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity, and axial diffusivity. Brain regions examined were restricted to the hippocampus (HC) and corpus callosum (CC).
Results: Significantly decreased fractional anisotropy (FA) was found in CC in mice at 27 months of age compared to 4 months, but not significant in other age groups. Mean diffusivity showed a tendency to decrease over age, however the changes were not shown with statistical significance when comparing various age groups. A decrease in axial diffusivity in CC of as much as 10% was found in the 27 months age group, but not so with in the radial diffusivity determination of the same comparison with any age groups. In contrast, FA measurements was shown to be increased in hippocampal region of mice at 27 months of age, which is not observed by other measurements in all age groups.
Conclusions: Overall, our data suggest that age-dependent changes induce significant axonal damage detected by DTI at extremely old age (27 months), with no detectable myelin damage in white matter as determined by the corpus callosum region in this study. In summary, DTI may be used as an imaging biomarker to monitor age-related degenerative process at extremely old mice, and thus providing the animal model for drug efficacy for intervention of this decline during normal aging as well as added disease related exasperation in the brain.
References:[1] Alexander, A.L., et al., Neurotherapeutics, 2007. 4(3): p. 316-29. [2] Bennett, I.J. and D.J. Madden, Neuroscience, 2014. 276: p. 187-205. [3] Sahara, N., et al., Neurobiology of Aging, 2014. 35(6): p. 1364-74. [4] Sun, S.W., et al., Experimental Neurology, 2005. 191(1): p. 77-85.

Disclosures: M. Zhu: None. **C. Akimana:** None. **E. Wang:** Other; Advanced Genomic Technology LLC, during the conduct of the study. **C.K. Ng:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.06/D7

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant NIA R01AG53274

Title: Aging-induced vascular damage of the mouse thalamus is associated with both motor and memory defects

Authors: *Y. WANG, E. TAYLOR, K. M. KANTAK, B. ZIKOPOULOS, F. SETA, N. HUANG, J. HAMILTON, K. MORGAN;
Boston Univ., Boston, MA

Abstract: Aging is a well-known risk factor underlying cardiovascular disease, but we know little about the effects of aging on the vasculature in the brain. We studied the relationship between aging and vascular damage in the brain of the mouse and correlated vascular changes with behavioral changes in motor and memory-related tasks across age groups. The present study included three age groups: 3 (young), 17-18 (middle-aged) and 24-25 (aged) month old C57B/6J male mice. We used a combination of histology (Prussian Blue staining, n=16) and MRI T2* imaging (n=9) to reveal the relationship between aging and vasculature damage in the brain. We conducted Novel Object Recognition tests (n=16) to test for cognitive defects associated with brain vascular damage. The histological data identified the mouse thalamus especially ventral posteromedial nucleus (VPM) and mediodorsal thalamic nucleus (MD), as the most vulnerable region for aging-induced microbleeds. The functional assay data indicated that vascular defects with aging may lead to motor and memory deficits in the mouse model. The MRI data also indicated the timeline of accumulation of thalamic microbleeds, and significant accumulation was first seen at middle-age, earlier than previously thought. The present study points to vascular disease as a possible factor as early as middle age in causing potentially irreversible brain damage.

Disclosures: Y. Wang: None. **E. Taylor:** None. **K.M. Kantak:** None. **B. Zikopoulos:** None. **F. Seta:** None. **J. Hamilton:** None. **K. Morgan:** None. **N. Huang:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.07/D8

Topic: C.01. Brain Wellness and Aging

Support: CONACyT Grants 634581
CONACyT Grants 252808

Title: Cerebrolysin treatment improves recognition memory and promotes an increase of BDNF and synaptophysin in an animal model of aging

Authors: *L. AGUILAR HERNÁNDEZ[1], A. DÍAZ[2], C. MORAN RAYA[3], G. FLORES[4];
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Mexico, Puebla, Mexico; [2]Benemerita Univ. Autonoma de Puebla / Facultad de Ciencias Químicas, Puebla, Mexico; [3]Benemerita Univ. Autonoma de Puebla / Inst. de Ciencias, Puebla, Mexico; [4]Benemerita Univ. Autonoma de Puebla / Inst. de Fisiología, Puebla, Mexico

Abstract: Aging is a normal process of living beings, characterized by a functional, metabolic and anatomical decline, which is caused by aging and inflicts molecular, cellular and systemic damage and eventually lead to the death of the organism. According to the WHO data, in the next decade, the world population of elderly people will increase from 12% to 22%. One of the factors that reduces the quality of life of this population is cognitive deterioration, which is the most common psychiatric pathology in this stage of life. Therefore, it is critical to have therapeutic tools that reduce cognitive deterioration due to aging. Cerebrolysin (CBL) is a preparation of neuropeptides derived from porcine brains that seems to mimic the action of endogenous neurotrophic factors in terms of brain protection and repair, which is supposed to help the cognitive decline that affects part of the senile population. In the present work, we evaluated the effects of CBL on cognitive performance in aged animals, C57BL6 mice of 18 month of age. Animals were treated with CBL (2 ml/kg i.p.) for 2 months. Then locomotive activity and recognition of novel objects test (NORt) were applied. After the behavioral tests, animals were sacrificed and the number of dendritic spines and types of spines of the pyramidal neurons of the prefrontal cortex, CA1, CA3 and dentate gyrus of the hippocampus and basolateral amygdala were analyzed. In addition, in the same regions, the levels of BDNF, synaptophysin, alpha-synuclein and nNOS were also analyzed. Finally, the number of cells were evaluated by stereology in the same regions. Our results showed that CBL improved the locomotor activity and memory processes in elderly animals. In addition, CBL also increased the BDNF and synaptophysin levels with higher numbers of cells in studied regions. In conclusion, our results suggest that CBL may be a good therapeutic tool in the treatment of cognitive decline of the senile population, because better cognition improves the quality of the life of the senile population (Supported by: CONACyT grants, No. 634581 to LAH and No. 252808 to GF).

Disclosures: **L. Aguilar Hernández:** A. Employment/Salary (full or part-time):; CONACYT. **A. Díaz:** None. **C. Moran Raya:** None. **G. Flores:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.08/D9

Topic: C.01. Brain Wellness and Aging

Support: MOST 107-2320-B-009-003-MY3

Title: A novel model to evaluate *Drosophila* cognitive status

Authors: *C.-C. YU[1], I.-Y. CHEN[2], F.-C. CHANG[2], C.-F. KAO[1,2,3];
[1]Inst. of Mol. Med. and Biochem. Engin., [2]Dept. of Biol. Sci. and Technol., [3]Ctr. For Intelligent Drug Systems and Smart Bio-devices (IDS2B), Natl. Chiao Tung Univ., Hsinchu, Taiwan

Abstract: Earlier studies in *Drosophila* indicate the fruit flies are equipped with sophisticated mechanisms to sense and evaluate the caloric content of various sugars. When presenting the starved fruit flies with two distinct sugar types, the sugar type with higher nutrient value (e.g. the nutritious sucrose vs. non-nutritious arabinose) is the preferred food source. Most importantly, the capability to read the nutrient value of sugars is independent of taste sensation, further suggesting the involvement of post-ingestion nutrient-sensing pathways, including the internal sensors and the computing neuronal circuits, which finalize the feeding decision based on the innate preference to nutritious and palatable food source. The entire computing processes of feeding decision in *Drosophila* can therefore be considered as a resolution of cognitive function. In this project, we exploited a distinct kind of behavior assay that monitors the changes of normal feeding decisions to determine the cognitive status of *Drosophila*. We first re-characterized the capability of *Drosophila* to read the caloric contents between distinct sugar types. Next, as an assessment of cognitive function, we also demonstrated the potential changes of feeding preference in animals with distinct conditions, such as animals with altered life expectancy and animals with neurodegenerative symptoms. Our results suggest the fruit flies lose the ability to discriminate nutritious substances when they pass certain chronological ages, which phenotype may represent the aging-related decline of cognitive functions. Moreover, while the feeding decision toward nutritious sugars is well retained in the genetically manipulated long-lived *Drosophila* at the old age, the disease flies quickly lose their ability to learn and evaluate the nutrient value of sugars along the disease progression. Together, our findings provide functional links between the accurate feeding decision and the cognitive status of *Drosophila*.

Disclosures: C. Yu: None. **I. Chen:** None. **F. Chang:** None. **C. Kao:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.09/D10

Topic: C.01. Brain Wellness and Aging

Title: The effect of lack of Annexin A1 on hypothalamic pituitary adrenal axis in a model of CORT-induced depressive like behaviour and the potential interaction with hippocampal memory

Authors: *R. CRUPI[1], A. PERITORE[1], E. GUGLIANDOLO[2], R. SIRACUSA[2], D. IMPELLIZZERI[2], R. FUSCO[2], M. CORDARO[2], R. D'AMICO[2], S. CUZZOCREA[2], R. DI

PAOLA[2];
[1]Univ. of Messina, Messina, Italy; [2]Univ. of Messina, MESSINA, Italy

Abstract: The activity of the hypothalamic-pituitary-adrenal axis (HPA) is commonly disregulated in stress-related psychiatric disorders. It was demonstrated that, in a family of sensor receptor of the immune system know as Formyl peptide receptors (FPR) specificly deficient mice for the Formyl peptide receptor 1 (FPR1) and Formyl peptide receptor 2/3 (FPR2/3), show a distinct profile of behaviour characterised by reduced anxiety. Annexin 1 (ANXA1), an endogenous ligand of FPR, is a member of the family of phospholipids and calcium annexes proteins with a well defined role in the delayed early inhibitory feedback of Glucocorticoids (GC) in the pituitary gland. The aim of the present study was first to evaluate the potential role of ANXA1 as a cellular mediator of behavioral disorders in a model of corticosterone (CORT) induced depression and, subsequently, the possible correlation between the depressive state and impairment of hippocampal memory. To induce the depression model, WT,ANXA1 KO and FPR2/3 KO mice, were exposed to CORT for 28 days. Behavioral tests were performed to test anxiety, depression like behaviour, anhedonia and recognition memory. ANXA1 KO mice showed an improvement in depression-like behavior compared to FPR2/3 KO and WT, after CORT administration. Several hippocampal marker for memory and depression, as well as the neurotrophic factors of BDNF and GDNF, pERK elevel and SERT expression, were analised to investigate the role of ANXA1 in the mechanism of action of GCs. In conclusion, we can state that the absence of the ANXA1 protein, even more than the absence of its main receptor (FPR 2/3), is is fundamental to the inhibitory action of GC on HPA axis, but also maintaining hippocampal homeostasis by preventing neuronal damage of chronic condition of depression.

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Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.10/D11

Topic: C.01. Brain Wellness and Aging

Support: University of Minnesota Kunin Professorship

Title: Longitudinal assessment of dynamic brain networks and cognition in healthy women

Authors: *A. P. GEORGOPOULOS[1,2], L. M. JAMES[3,2], S. DOLAN[2];
[1]Neurosci., Univ. Minnesota, Minneapolis, MN; [2]Brain Sci. Ctr., Minneapolis Hlth. Care Syst., Minneapolis, MN; [3]Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: We assessed longitudinally cognitive and brain function in 87 healthy women. Participants were enrolled at age 33-96 y, when they had a Montreal Cognitive Assessment (MoCA) score of 25 or greater. Participants were assessed annually (up to 7 years currently) for their cognitive function (MoCA) and for their brain function using magnetoencephalography (MEG). Participants underwent a 1-min resting-state MEG scan using a 248 axial gradiometer system (Magnes 3600WH, 4-D Neuroimaging, San Diego, CA) at a sampling rate of 1017 Hz (i.e. every 0.983 ms). Zero-lag cross-correlations were obtained between all pairs (N = 30628) of prewhitened MEG time series (Synchronous Neural Interactions, SNI [1]). In a recent study [2] we showed that the standard deviation (SD) of the absolute value of SNIs increases with age. In a separate presentation at this meeting [3] we report that SD covaries negatively with MoCA score, such that higher SD values are associated with lower MoCA score. Here we investigated possible SD-MoCA covariation over the period of longitudinal testing at additional 50 lags (~50 ms) of the Cross-Correlation Function (CCF). We found that a negative correlation between SD and MoCA that was stronger and highly statistically significant at CCF lags greater than 8 ms. This indicates that the dynamic brain mechanisms underlying cognitive function operate as a lagged neural network [4], a reasonable suggestion, given that all neural interactions are carried out through fiber tracts with specific, non-trivial conduction velocities. From this perspective, the longer lags above indicate the intimate involvement in cognitive function of relatively slowly-conducting fiber tracts, on the average. Given the diversity of axonal thickness in the cortex (which determines conduction velocity) and its dependence on the origin and the destination of the projection [4], a detailed topographic analysis of the lags of specific interactions (e.g. callosal vs. intrahemispheric) at which significant relations to the MoCA score occur would provide new insights in understanding neural-cognitive processing. (Supported by the University of Minnesota's Kunin Professorship in Women's Healthy Brain Aging to Lisa M. James.) 1. Georgopoulos et al. (2007) J Neural Eng 4:349-355. 2. James et al. (2018) EBioMedicine 35:288-294. 3. Dolan et al. (2019) Cross-sectional and longitudinal assessment of cognitive function in healthy women (This meeting). 4. Caminiti et al. (2009) PNAS 106:19551-19556. 5. Innocenti et al. (2014) Cereb Cortex 24:2178-188.

Disclosures: A.P. Georgopoulos: None. **L.M. James:** None. **S. Dolan:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.11/DP04/D12

ControlExtraData.DynamicPosterDisplay:

Dynamic Poster

Topic: C.01. Brain Wellness and Aging

Support: AG003649

Title: Multiphoton imaging reveals that a microglial response to microinjury is elevated in hippocampal white matter and inhibited by glucocorticoid

Authors: J. C. GANT, O. THIBAULT, ***E. M. BLALOCK**;
Univ. Kentucky Coll Med., Lexington, KY

Abstract: Quantifying whether microglial show an 'aggressive', a 'normal', or a 'quiescent' response to brain damage is an area of some debate because microglial responses are highly dependent on their environment. Dynamic responses can be measured *in vitro*, but the *in vitro* preparation itself alters microglial behavior. Post-mortem measures capture the native environment, but lose dynamic responses. Finally, damage magnitude matters. Many experimental models involve large injuries, while many conditions (e.g., microbleeds) induce microscopic changes. Here, we addressed some of these issues by developing a 'microglial response to microinjury' (MRMI) assay. This method images living microglia in an *ex vivo* environment that closely matches microglial native environment, induces a microscopic injury, and quantifies response. CX3cr1-GFP mouse (produce green fluorescent protein in microglia/ macrophages) hippocampal slices are imaged and a small 30x20 um cylindrical avulsion (microinjury) is created. The resulting MRMI is rapid (5-20 min), quantifiable, elevated in white matter, and inhibited by glucocorticoid, consistent with prior reports. Thus, this method appears appropriate for not only assessing the microglial response to microinjury in the context of various disease states, but also in the context of dissecting out the pharmacology of its facilitation or inhibition by different agents.

Disclosures: J.C. Gant: None. **O. Thibault:** None. **E.M. Blalock:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.12/D13

Topic: C.01. Brain Wellness and Aging

Support: Netherlands Organisation for Scientific Research, Veni grant: 016.136.072

Title: The effect of cognitive function, subjective cognitive decline, and vascular risk on white matter hyperintensity change in older adults

Authors: *Y. JUNG, R. P. VIVIANO, J. S. DAMOISEAUX;
Wayne State Univ., Detroit, MI

Abstract: White matter hyperintensities (WMH), a manifestation of cerebral small vessel disease often observed in magnetic resonance imaging (MRI) brain scans of older adults, have been associated with cognitive function, subjective cognitive decline (SCD), and vascular risks. Recent studies showed that the WMH in different white matter tracts are uniquely associated with different domains of cognition, but it is still unclear how longitudinal changes of tract-specific WMH are associated with cognitive function, SCD, and vascular risks. A total of 91 healthy late middle-aged to older adults (m: 57, f: 34; age = 67.8±8.3) recruited in two locations (US and Netherlands) participated in this study. Out of the 91 participants, 69 returned for a follow-up session after 18 months. We assessed WMH volume of the anterior thalamic radiation (ATR), forceps minor (Fmin), superior longitudinal fasciculus (SLF), and whole brain on FLAIR MRI images using the lesion prediction algorithm in LST toolbox with manual correction. We measured cognitive function using the Trail Making Test, Digit Symbol-Coding test, and Stroop task, and SCD using the Frequency of forgetting (FoF) scale of the Memory Functioning Questionnaire. As an indicator of vascular risks, we used mean arterial pressure (MAP). To examine the association between WMH volume, cognition, FoF, and MAP we performed linear regression. To examine the association between longitudinal WMH change and cognition, FoF, and MAP we ran linear mixed models. Test site, age, and gender were included as covariates in all models. Lower TMT-A score, a measure of processing speed, was associated with higher WMH volume in the ATR (p = .003), Fmin (p = .003), and whole brain (p = .016). Greater FoF was associated with higher WMH volume in the whole brain (p = 0.004) and ATR (p < 0.001). Higher MAP was related to higher WMH volume in the whole brain (p = .028) and SLF (p = .003). WMH volume of the ATR, Fmin, and whole brain increased over time (all ps < .001). Neither tract-specific nor whole brain WMH volume change was predicted by baseline SCD or cognitive function. However, higher baseline MAP predicted a steeper increase of whole brain WMH (p = .028) over time. Our cross-sectional analyses revealed that cognitive performance, SCD, and MAP were associated with WMH burden, which is consistent with previous findings. However, our longitudinal analyses found that only higher baseline MAP was predictive of WMH increase, and that this effect was whole brain rather than tract-specific.

Disclosures: Y. Jung: None. **R.P. Viviano:** None. **J.S. Damoiseaux:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.13/D14

Topic: C.01. Brain Wellness and Aging

Title: Age-associated impairments in trace eyeblink conditioning occur earlier in the lifespan than previously suspected

Authors: *R. WEST, P. MAXHAM, L. THOMPSON;
Behavioral and Brain Sci., Univ. of Texas at Dallas, Richardson, TX

Abstract: Eyeblink conditioning (EBC) is a simple and well-established model to assess learning in aging across species. Intact hippocampal function is required for successful acquisition of the trace EBC paradigm. While impairments in trace EBC are well established in advanced age groups (greater than 65 yr of age), the purpose of the current study was to cross-sectionally examine the onset and severity of age-associated learning impairments in acquisition of trace conditioning in individuals aged 19 to 88 yr.
79 healthy individuals, between the ages of 19 and 88 yr (31 male, 48 female) were recruited to perform EBC tasks, and divided by deciles of age (i.e. 30-39, 40-49 yr). All subjects had normal hearing. Sixty trials each were presented using the trace 500 conditioning paradigm. An airpuff (150 ms, 3 psi) applied to the left cornea served as the unconditioned stimulus (US), and a tone (100 ms) served as the conditioned stimulus (CS), separated by a 500 ms interstimulus trace interval. An infra-red detection system was used to blindly score performance on each trial, and inter-trial intervals were pseudorandomly varied. Mean percent adaptive conditioned responses (ADT-CRs; i.e. appropriately timed eyeblinks to shield the cornea from the airpuff) served as a primary measure of task acquisition. Percent of ADT-CRs were compared within and between age groups using one-way ANOVA and Tukey's post-hoc comparisons.
No significant sex-differences were found in average percent of ADT-CRs comparing between males and females across age groups ($p=0.64$). 20- and 30-year-olds exhibited similar high percentages of ADT-CR acquisition ($p=0.8$) and performed significantly better than older cohorts ($p=0.01$). Interestingly, a functionally significant deficit in trace EBC task acquisition was observed in the age decade beginning in the 40s. In further analyses of 40 yr old and older individuals, additional criteria were assessed, including trials-to-40% CRs. After 40 yr of age, impairments in acquisition were observed early in training (before trial 25) in growing subpopulations compared to younger subjects, suggesting a significant timing-dependent effect on overall task acquisition. Potential clinical implications are discussed.

Disclosures: R. West: None. **P. Maxham:** None. **L. Thompson:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.14/D15

Topic: C.01. Brain Wellness and Aging

Support: NSERC RGPIN-2016-05991

NIMH 5R01MH111099
NIH MH111099
NIH GM076990
UBC Bioinformatics Graduate Training Program
KBHN/NCE

Title: Identification of cell type proportion changes in bulk brain expression profiles

Authors: *O. MANCARCI[1], L. TOKER[2], S. TRIPATHY[3], P. PAVLIDIS[4];
[1]Psychiatry, Univ. of British Columbia, Vancouver, BC, Canada; [2]Universty of Bergen, Bergen, Norway; [3]Psychiatry, Univ. of Toronto, Toronto, ON, Canada; [4]Psychiatry, Univ. British Columbia, Vancouver, BC, Canada

Abstract: Differential expression in whole tissue expression profiles are often used to study neurological disorders. In such studies, differential expression can be a result of a uniform change in gene expression of all cell types, gene expression changes in specific cell types, or changes in cell type proportion. In this study we use our previously published method for detecting cell type proportion changes in bulk tissue brain expression profiles. Our method summarizes gene expression of cell type markers to get an estimate of cell type proportion changes. We use this method to analyze ~800 mouse and human brain bulk tissue datasets from the literature to identify conditions cause changes in cell type proportions. We also expand this method to include robust quality metrics to reliably separate gene regulation from changes in cell type proportions and identify false positive findings. We identify known cell type proportion changes in neurodegeneretive disorders along with novel changes under a wide variety of conditions ranging from neurological disorders in humans to mouse models.

Disclosures: O. Mancarci: None. **L. Toker:** None. **S. Tripathy:** None. **P. Pavlidis:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

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Program #/Poster #: 470.15/D16

Topic: C.01. Brain Wellness and Aging

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CNPq 303283/2014-9
CNPq 425838/2016-1
CNPq 307252/2017-5
CAPES 086/2013

Title: Neuroprotective effects of kinin B2 receptor in organotypic hippocampal cultures of middle aged mice

Authors: *M. TORICELLI[1], S. EVANGELISTA[1], L. OLIVEIRA[1], T. VIEL[2], H. BUCK[1]; [1]Faculdade De Ciências Médicas Da Santa Casa De São, São Paulo, Brazil; [2]Univ. de São Paulo, São Paulo, Brazil

Abstract: Aging is a multifactorial phenomenon that results in several changes at cellular and molecular levels and is considered the main risk factor for some neurodegenerative diseases. Several evidences show the participation of the kallikrein-kinin system in neurodegeneration and this system has been associated with inflammation and immunogenic responses in the central and peripheral systems by the activation of the B1 and B2 receptors. Previous work by our group showed that bradykinin and the B2 receptor played a possible role in neuroprotection. Therefore, the objective of this study was to evaluate the participation of B2 receptors in cell viability, neuroinflammatory response and neuroplasticity in organotypic hippocampal cultures of 6 and 12 month old mice. It was observed that activation of the B2 receptor by bradykinin decreased the inflammatory response and increased plasticity in 12 months old slices. Conversely, there was an increase in the inflammatory response and a decrease in neural plasticity in the six-months old slices. In both ages an increase in cell viability was observed. Our data indicated that the kallikrein kinins system only plays a neuroprotective role in middle-aged animals, that is, in a context in which the aging process and neuroinflammation is already established.

Disclosures: M. Toricelli: None. **H. Buck:** None. **S. Evangelista:** None. **L. Oliveira:** None. **T. Viel:** None.

Poster

470. Brain Wellness and Aging: Mechanisms and Biomarkers

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 470.16/D17

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: An app a day keeps the doctor informed: Development of smart-device applications as early diagnostic tools to detect hippocampal pathology in adolescent binge drinkers

Authors: A. GALUSHA, A. M. PREUSS, *P. A. BLANKENSHIP; Lewis Univ., Romeoville, IL

Abstract: The ability to effectively navigate through one’s environment is a critical facet in everyday life. Maintaining spatial orientation involves utilizing a variety of spatial cues. In particular, spatial information can be divided into two main types: environmental cues, which include any visual, auditory, or olfactory cues, or self-movement cues, which include

proprioception, vestibular information, and optic flow. The structures that support spatial processing, such as the hippocampus, are especially vulnerable to environmental factors, like alcohol, during the adolescent critical period of development. For example, previous work has shown that a binge drinking pattern of alcohol consumption during adolescence is associated with structural and functional changes in the hippocampus. More recently, self-reports of binge drinking have been associated with impaired performance on hippocampal-dependent spatial tasks. The current study sought to replicate these findings and extend this work by implementing a novel application-based analogue to previously developed spatial tasks. University undergraduates identified as binge drinkers or non-binge drinkers were subsequently tested on an application analogue of the previously developed manipulatory-scale dead reckoning task (DRT). The accuracy of the return trip was examined using a number of measures, including path circuity as well as heading and distance error. While data collection is ongoing, preliminary data suggests an impaired homing accuracy, associated with higher heading and distance errors, in self-reported binge drinkers. These results provide the foundation for developing diagnostic tools for detecting hippocampal pathology.

Disclosures: **A. Galusha:** None. **A.M. Preuss:** None. **P.A. Blankenship:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.01/D18

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

Support: Univ. of Kentucky Dept. of Neuroscience

Title: The effects of fragmentation of the daily sleep-wake rhythm on amyloid-beta levels and neuroinflammation in the 3X Tg-AD mouse model of Alzheimer's disease

Authors: *M. J. DUNCAN[1], E. ASKAROV[1], A. BAKER[1], L. BEECHEM[1], B. D. GILLIS[2], F. SALISBURY[3], L. E. GUERRIERO[3], B. F. O'HARA[3], A. D. BACHSTETTER[1], M. P. MURPHY[2];
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Abstract: In older humans, fragmentation of the daily sleep-wake rhythm is correlated with the risk of development of Alzheimer’s disease (AD). While sleep deprivation for many consecutive hours increases brain amyloid-beta (Aβ) levels and neuroinflammation, the effects of chronic fragmentation of the daily sleep-wake rhythm are unknown. The present study tested the hypothesis that chronic fragmentation of the daily sleep-wake rhythm stimulates brain amyloid-beta (Aβ) levels and neuroinflammation in the 3XTg-AD mouse model of AD. Female 3XTg-

AD mice (8 months old) were subjected to chronic sleep fragmentation (SF; N=8) or undisturbed sleep (SF; N=8) for 4 weeks. SF consisted of 4 daily sleep disruptions (1 h ea) evenly distributed during the light phase. During SF, mice were kept awake with novel objects and gently simulation with a paintbrush. Mice were individually housed in PiezoSleep cages (Signal Solutions LLC) for sleep recordings during the 1rst and 4th weeks of the study and group-housed in regular cages during the 2nd and 3rd weeks. Compared to US mice, SF mice exhibited lower levels of light phase sleep (17.7% reduction, $P<0.001$) and higher levels of dark phase sleep (14.8% increase, $P<0.05$), with an overall decrease in total 24-h sleep (3.5% reduction, $P<0.001$). After 4 weeks, the mice were euthanized under anesthesia and hippocampal tissue was harvested and stored at -80 C. One hippocampal half was extracted in standard RIPA buffer and Aβ was measured by ELISA (Invitrogen $A\beta_{40}$, KHB3841, or $A\beta_{42}$, KHB3544). Aβ levels were higher after SF vs US (Aβ40: (1.96 ± 0.10 vs 1.63 ± 0.10, $p<0.05$ and Aβ42: 1.48 ± 0.20 vs 0.90 ± 0.10, $p<0.01$). mRNA was isolated from the other hippocampal half and TaqMan low-density gene expression array was conducted for markers of microglial activation (ctsd, cst7, and clec7a) and proinflammatory cytokines (TNFα, IL6, and IL-1β). The composite Z-scores for microglial activation markers and proinflammatory cytokines were significantly higher ($P<0.05$) in the SF than the US hippocampal tissue. These findings demonstrate a protocol for fragmenting the daily sleep-wake rhythm in 3X-Tg AD mice. The results support the hypothesis by revealing that sleep fragmentation for 4 weeks increases hippocampal levels of Aβ40 & Aβ42 and expression of microglial activation markers and proinflammatory cytokines. These studies support the concept that improving sleep consolidation in individuals at risk for AD may be beneficial for slowing the onset or progression of this disease, but more studies are needed to further investigate how sleep fragmentation affects neuropathology in both male and female AD mice.

Disclosures: **M.J. Duncan:** None. **E. Askarov:** None. **A. Baker:** None. **L. Beechem:** None. **B.D. Gillis:** None. **F. Salisbury:** None. **L.E. Guerriero:** None. **B.F. O'Hara:** 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.; Jazz Pharmaceuticals; Signal Solutions LLC. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signal Solutions LLC; Gismo Therapeutics. F. Consulting Fees (e.g., advisory boards); Gismo Therapeutics. **A.D. Bachstetter:** None. **M.P. Murphy:** 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.; GISMO Therapeutics.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.02/D19

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

Title: Effects of chronic sleep restriction on amyloid beta and cognition in C57BL/6 mice

Authors: K. N. BRICE[1], C. W. HAGEN[2], J. L. PETERMAN[1], P. N. BRADEN[1], J. W. FIGG[2], M. J. CHUMLEY[2], G. W. BOEHM[1];
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Abstract: Alzheimer's Disease (AD) is the 6th leading cause of death in the US. More than 44 million people worldwide, including 5.7 million Americans, are living with this neurodegenerative disease, and those numbers continue to climb. One rarely discussed feature of AD is a disrupted sleep/wake cycle. Sleep is essential for many psychological and biological functions, and a reported 35.3% of adults get less than the minimum 7 hours of sleep per night recommended by the National Sleep Foundation. Moreover, evidence suggests a bidirectional relationship between sleep loss and AD. Previous research indicates that disruptions in sleep often precede symptoms of AD such as cognitive impairments and memory loss. Additionally, sleep loss has been associated with increased amyloid-beta and proinflammatory cytokines in the brain. Prolonged elevations in these proinflammatory cytokines are associated with enhanced amyloid beta production, which accelerates the formation of oligomers and plaques that disrupt synaptic function. The aim of the present study was to elucidate the interaction between chronic sleep restriction, inflammation, and AD pathology in C57BL/6 mice. Our lab has previously demonstrated that mice administered 7 consecutive days of LPS, a bacterial mimetic, exhibit increases in amyloid beta and proinflammatory cytokines in the brain, as well as cognitive deficits. Furthermore, research from our lab has shown that stress can exacerbate the effects of LPS. Adult C57BL/6 mice were subjected to the multiple platform method of sleep disruption for 10 hours per day for 6 weeks. After receiving 7 consecutive days of either LPS or saline injections, animals were subjected to contextual fear conditioning to assess cognitive functioning, after which hippocampal amyloid beta levels were quantified. Although LPS administration failed to increase amyloid beta or cognitive deficits in contextual fear conditioning, chronic sleep restriction itself was associated with deficits in contextual fear acquisition and increased levels of hippocampal amyloid beta compared to control groups. These findings suggest that chronic sleep loss may have a detrimental effect upon cognitive function through increasing amyloid beta levels in the hippocampus, even in wild-type mice. Given the large percentage of adults reporting less than the minimum recommended amount of sleep per night, the alarming climb in rates of AD, and a growing body of work suggesting a link between sleep loss and AD, investigating the detrimental effects of sleep restriction is essential.

Disclosures: **K.N. Brice:** None. **C.W. Hagen:** None. **J.L. Peterman:** None. **P.N. Braden:** None. **J.W. Figg:** None. **M.J. Chumley:** None. **G.W. Boehm:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.03/D20

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

Support: Ruth K. Broad Foundation

Title: Selective activation of the thalamic reticular nucleus restores sleep patterns but does not affect epileptic activity in Alzheimer's disease mice

Authors: *R. JAGIRDAR[1], F. M. SEIBT[2], M. BEIERLEIN[2], J. CHIN[1];
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Abstract: Alzheimer's disease (AD) is associated with memory impairment, cognitive dysfunction, sleep fragmentation and increased incidences of unprovoked seizures, both nonconvulsive and convulsive. These seemingly disparate symptoms are observed also in transgenic mouse models of AD and have in common the fact that they can be regulated by activity in the corticothalamic network. The thalamic reticular nucleus (TRN) is a major control nucleus in this network and is implicated in spike-wave discharges and seizures in absence seizure models. Since we previously found that activity in TRN is reduced in transgenic mice that express human amyloid precursor protein (APP), a well-characterized mouse model to study AD, we investigated whether restoring activity in the TRN affects the incidence of epileptic spikes or seizures, sleep architecture, or accumulation of Abeta, which has been shown to be modulated by sleep. Selective activation of TRN in APP mice was achieved using viral expression of DREADDs. Activation of the excitatory DREADD hM3Dq using CNO was confirmed both *in vivo* by measuring immunoreactivity of a marker of neuronal activity and *in vitro* using thalamic slices. In APP mice expressing hM3Dq (APP-hM3Dq), acute activation of TRN with a single dose of CNO increased slow wave sleep and reduced sleep fragmentation, with no effect on the frequency or duration of seizures. Chronic treatment of APP-hM3Dq mice with CNO for 30 days reduced sleep fragmentation for the duration of treatment and decreased Aβ plaque accumulation, relative to APP-hM3Dq treated with saline for 30 days. Chronic activation of TRN also had no obvious effects on seizures. These results indicate that selective activation of the TRN is sufficient to restore sleep maintenance and slow wave sleep, with no obvious effects on seizures.

Disclosures: **R. Jagirdar:** None. **F.M. Seibt:** None. **M. Beierlein:** None. **J. Chin:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.04/D21

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

Support: NIH NS085171 (JC)

Title: Seizure-induced ΔFosB binds target genes in both disease-dependent and independent manners

Authors: *G. S. STEPHENS[1], Y. ZHENG[1], C.-H. FU[1], J. J. BOTTERILL[2], J. J. LAFRANCOIS[2], H. SCHARFMAN[2,3], Y. LIU[4], J. CHIN[1];
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Abstract: The incidence of seizures is increased in Alzheimer's disease (AD), and treatment of AD patients with the antiepileptic levetiracetam improves cognition. We reported that one mechanism by which seizures exert long-lasting effects on cognition is through expression of ΔFosB, a transcription factor with an unusually long half-life. Even infrequent seizures in transgenic mice expressing human amyloid precursor protein (APP) lead to persistent increases in ΔFosB in the hippocampus, similar to what we observed in patients with either AD or temporal lobe epilepsy. ΔFosB epigenetically regulates expression of target genes; however, whether ΔFosB targets the same genes when induced by seizures in different neurological conditions is not clear. We performed ChIP-sequencing to assess the landscape of ΔFosB target genes in APP transgenic mice versus pilocarpine-treated wildtype mice (Pilo mice), a pharmacological model of epilepsy. These mouse models allowed us to compare AD, in which seizures occur in the context of high levels of amyloid beta, and epilepsy, in which recurrent seizures occur in the absence of neurodegenerative conditions. Network profiling of genes bound by ΔFosB in APP mice, Pilo mice, and respective control mice revealed that regulatory programs modulated by ΔFosB in the hippocampus are expanded and diversified in APP and Pilo mice (vs respective controls). Clustering analyses demonstrated that functions related to neuronal development and neurogenesis were consistently represented in ΔFosB target gene networks in all groups of mice (APP mice and nontransgenic controls, Pilo mice and saline controls). However, in both APP mice and Pilo mice, but not their controls, ΔFosB target pathways also included domains of neuronal excitability and plasticity, and glutamatergic signaling. Notably, there were also functional domains that were represented only in APP mice or only in Pilo mice. Our findings indicate that seizure-induced ΔFosB targets some genes regardless of disease

context, but targets others in a disease context-specific manner. Understanding what factors underlie these differences, such as chromatin accessibility or abundance of transcriptional binding partners, could reveal novel insights into the control of gene expression in neurological disorders.

Disclosures: **G.S. Stephens:** None. **Y. Zheng:** None. **C. Fu:** None. **J.J. Botterill:** None. **J.J. LaFrancois:** None. **H. Scharfman:** None. **Y. Liu:** None. **J. Chin:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.05/D22

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

Support: WV Clinical and Translational Science Institute Pilot Project Award
National Institutes of Neurological Disorders and Stroke NS111541

Title: Increased excitability of somatostatin-containing cortical interneurons in presymptomatic AD mice

Authors: H. HU[1], ***A. AGMON**[2];
[1]Dept. of Neurosci., West virginia Univ. Sch. of Med., Morgantown, WV; [2]Dept. of Neurosci., West Virginia Univ. Sch. of Med., Morgantown, WV

Abstract: Alzheimer’s disease (AD) is a devastating, progressive dementia with no known prevention or cure. All efforts to-date to reverse or arrest disease progression have failed, possibly because they were applied too late in the disease process, when irreversible damage to cortical networks has already occurred. Thus, a better understanding of the earliest, presymptomatic stages of the disease is critically needed if we are to develop successful interventions. A consistent finding in human AD patients, postmortem human AD tissue and mouse models of AD, is specific loss of somatostatin-containing (SOM) inhibitory interneurons and synapses in the cerebral cortex. We hypothesized that the normal functioning of SOM interneurons is disrupted very early in the progression of AD, well before the neurons die and before any of the histological or behavioral manifestations of the disease are evident, and that this dysfunction may play a facilitatory role in disease progression. If so, then early interventions which prevent SOM interneuron dysfunction would be highly promising as anti-AD therapies. Using whole-cell recordings in cortical brain slices, we characterized the electrophysiological properties of SOM interneurons in TgCRND8 mice, a transgenic mouse model which expresses a human amyloid precursor protein with familial AD mutations. Brain slices were prepared from 2-4 week old animals, before any pathological or behavioral changes are evident in this mouse model. To identify SOM interneurons, transgenic mice were crossed with mice expressing GFP

in specific populations of SOM interneurons. We compared electrophysiological parameters of SOM interneurons from transgenic animals to those from wildtype littermates, and performed the same comparison for fast-spiking (FS) cells, a separate interneuron subclass. Comparisons were done while blinded to genotype. In SOM, but not in FS interneurons, we found a ~50% decrease in the minimal current level generating an action potential (rheobase). This implies a doubling of the intrinsic excitability of these interneurons, with a possible outcome of increased Ca^{2+} influx, potentially leading to excitotoxic cell death. To our knowledge this is the first report of profound changes in the intrinsic physiology of inhibitory interneurons in pre-symptomatic AD mice.

Disclosures: H. Hu: None. **A. Agmon:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.06/D23

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

Support: CAPES
FAPESP (17/23169-1)

Title: Effect of thyroid hormones on the behavior of 3xTg-AD mice (APPswe, PS1m146v, tauP301L) model of Alzheimer's disease

Authors: *A. V. MAGLIONE[1], B. P. P. DO NASCIMENTO[2], T. J. LEITE[3], F. B. LORENA[2], M. O. RIBEIRO[4], C. A. A. PENATTI[5], R. R. DA CONCEIÇÃO[3], M. A. SATO[6], J. S. DE SOUZA[3], G. GIANNOCCO[3];
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Abstract: Background: Alzheimer disease (AD) is the most frequent cause of dementia, compromising cognitive and behavioral functions. Its establishment is due to the accumulation of genetic, environmental and metabolic events. It is known that the central nervous system is an important target of thyroid hormones (TH) and evidence shows that thyroid status can modulate the appearance of AD. Aim: to investigate the effect of treatment with T3 and Methimazole in behavior and gene expression of neurotrophins and AD markers in male transgenic mices 3xTg-AD. Materials and Methods: Male 3xTg-AD mices (~30g, N=6, approved by Animal Ethics Committee- CEUA nº 1880171017) were divided into 3 groups, all treated with intraperitoneal injections: (1) treated with T3 (20-30 ng/g of L-T3, physiological dose 5x); (2) treated with

Methimazole (0.05%, 5mg/100g animal body weight); (3) treated with saline solution (control group). At the 15º day of treatment the following tests were applied: Open Field, Elevated Plus Maze, Marble Burying, Tail Suspension and Forced Swimming. One day after the tests, animals were anesthetized with ketamine and xylazine, the brain was harvest and frozen in liquid nitrogen for RT-qPCR analysis. Total RNA of hippocampus was extracted and the gene expression of ADAM10, GSK3, BDNF, NTF3, NGF, GAD65, GAD67, SERT, TPH2, 5HT1A, BMP-7 and SOD2 was carried out by qPCR. Data were analyzed by relative gene expression and were represented as mean ± SEM, and submitted to unpaired Student t-test ($p<0.05$) and was analyzed by Pearson Correlation. Results: Gene expression of GSK3 was significantly reduced in T3 group (0.5930 ±0.1125) compared with saline (1.00 ±0.1083), ADAM10 was significantly reduced in T3 group (0.5119 ±0.1168) compared with saline (1.00 ±0.1215). Expression of BMP-7 was reduced in T3 group (0.5515 ±0.0616) compared with saline (1.00 ±0.08402) and SOD2 was increased in T3 group (2.355 ±0.4314) compared with saline (1.00 ±0.056). In forced swim test the animals treated with T3 decreased the fluctuation time (53.0 ±9.950) compared with saline (124.5 ±9.937) and in tail suspension test the animals treated with T3 decreased the immobilization time (64.60 ±17.19) compared with saline (132.5 ±18.31). In addition, a negative correlation between behavior tests and gene expression of genes related to GABA and serotonin in Pearson Correlation was observed. Conclusion: There was a decrease in depressive behavior and expression of genes related to APP production, β-amyloid peptide production and tau phosphorylation in animals
treated with T3 when compared with control saline group. The data suggest an important role of TH in the modulation of AD and depressive behavior.

Disclosures: **A.V. Maglione:** None. **B.P.P. do Nascimento:** None. **T.J. Leite:** None. **F.B. Lorena:** None. **M.O. Ribeiro:** None. **C.A.A. Penatti:** None. **R.R. da Conceição:** None. **M.A. Sato:** None. **J.S. de Souza:** None. **G. Giannocco:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.07/D24

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

Support: FIS/IMSS/PROT G15/1397

Title: Evaluation of the integrity of the blood-brain barrier during the progression of Alzheimer's disease in the 3xTg-AD model

Authors: ***A. ISLAS**[1], M. BERNABE[2], P. GARCIA-DELATORRE[3];
[1]Inst. Mexicano del Seguro Social, Mexico, Mexico; [2]IMSS, Mexico, Mexico; [3]IMSS-UIM Enfermedades Neurológicas, Mexico city, Mexico

Abstract: Alzheimer's disease is the most common cause of dementia worldwide. This is characterized by the accumulation of two proteins mainly: tau in its hyperphosphorylated form, which accumulates forming neurofibrillary tangles and beta amyloid, which accumulates forming plaques. This accumulation starts in brain areas relevant to the formation and maintenance of memory, so, clinically, the main feature of AD is cognitive deficit, however, by the time these symptoms are visible, the disease is already in a relatively advanced stage. It is also known that when the neurofibrillary plaques and tangles become detectable, it is because there was already a previous neurodegenerative process, which is speculated to have to do with a compromise of the integrity of the blood-brain barrier.The triple transgenic murine model (3xTg-AD) that we propose to use in this project develops aggregates of both Aβ and Tau, a characteristic described in the development of AD in humans. This allows us to evaluate if there is an effect of mutations in APP (amyloid precursor protein), Tau and presenilin (PSEN1 and PSEN2) that are affecting the microvasculature in AD. Likewise, we can evaluate the effects of the accumulation of Aβ and tau, pathology that describes from its origins to the EA. Murine models for AD with mutations in APP have already described differences in microvessels such as aggregates of Aβ, hindered microcirculation, etc. In fact, some studies have used the 3xTg-AD model in which they describe a decrease in cerebrovascular volume and an increase in collagen I and IV. In this study we aimed to determine if there are changes in the microvessels at different stages of the progression (3,6, 9 and 13 months) of Alzheimer's disease in a transgenic triple murine model (3xTg-AD) by means of western blot analysis of tight junction proteins. We found that there are differences in the protein composition of the microvessels in the transgenic animals compared to the control animals, as well as that there is a decrease in the amount of protein from the tight junctions during progression.

Disclosures: A. Islas: None. **M. Bernabe:** None. **P. Garcia-delaTorre:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.08/D25

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

Support: FDA/NCTR protocol E07631.01

Title: Impaired aβ clearance leads to vascular dysfunction in a transgenic model of Alzheimer’s disease

Authors: *H. ROSAS-HERNANDEZ[1], E. CUEVAS[3], J. B. RAYMICK[4], B. ROBINSON[2], S. SARKAR[5];
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Abstract: Alzheimer's disease (AD) is the most common type of dementia, affecting approximately 5.8 million Americans. The pathological findings in AD include amyloid plaques containing amyloid beta (Aβ) peptides and neurofibrillary tangles containing hyperphosphorylated tau protein. In addition to neuronal loss, cerebral amyloid angiopathy (CAA) occurs in AD. CAA is characterized by Aβ deposition in the brain microvessels, which leads to increased blood-brain barrier (BBB) permeability and vascular dysfunction, further exacerbating AD pathology. The present study characterized brain vascular function in the Tg-SwDI mouse model of AD which expresses the amyloid precursor protein Swedish K670N/M671L and vasculotropic Dutch/Iowa E693Q/D694N mutations. We isolated brain capillaries from 13-month old Tg-SwDI and wild type (WT) mice and used Western and dot blot analyses to determine the expression of monomeric and aggregated forms of Aβ, P-glycoprotein (P-gp), the receptor for advance glycation end-products (RAGE) and the tight junction (TJs) proteins occludin and claudin-5. In addition, we isolated and cultured brain endothelial cells to analyze barrier function via fluorescein flux. Results indicated that aggregated and oligomeric forms of Aβ are increased in brain capillaries of Tg-SwDI mice compared to WT animals. In addition, the efflux transporter P-gp was decreased in Tg-SwDI mice, while RAGE (which transports Aβ peptides from blood to brain) was increased. Moreover, the TJ protein occludin was decreased in Tg-SwDI mice, while claudin-5 remained unchanged. A decrease in the expression of occludin was related to an increase in BBB permeability in isolated brain endothelial cells in culture, as evidenced by an increase in fluorescein flux through the endothelial monolayer. These findings demonstrated that, in Tg-SwDI mice, impaired Aβ clearance, driven by a decrease in P-gp and an increase in RAGE, leads to the accumulation of aggregated and oligomeric Aβ in the brain capillaries. This accumulation promotes a decrease in the expression of the TJ protein occludin and as consequence, an increase in BBB permeability. Additional studies are underway to analyze the contribution of vascular dysfunction to the progression of AD pathology

Disclosures: H. Rosas-Hernandez: None. **E. Cuevas:** None. **J.B. Raymick:** None. **B. Robinson:** None. **S. Sarkar:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.09/D26

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

Support: Beca CONACyT 612139

Dirección General de Asuntos del Personal Académico, UNAM, Mexico (Grant IN202018)
CONACyT; Grant # A1-S-7540

Title: Sudden intrabulbar amyloid beta increase simultaneously disrupts olfactory bulb oscillations and odor detection

Authors: *R. H. SOTO, K. ROJAS GARCIA, J. PEÑA ORTEGA;
Dept. de Neurobiología del Desarrollo y Neurofisiología, Univ. Nacional Autónoma de México, Queretaro, Mexico

Abstract: There seems to be a correlation between soluble amyloid beta protein (AB) accumulation in the main olfactory bulb (OB) and smell deterioration both in Alzheimer Disease (AD) patients and animal models. Moreover, this smell-loss seems to be related to alterations in neural network activity in several olfactory-related circuits, including the OB, which is observed both in anesthetized animals and brain slices. It is possible that there is a correlation between these two pathological phenomena but, a direct and simultaneous evaluation of the acute and direct effect of AB on the OB activity while animals are actually smelling has not been performed. Thus, here we tested the effects of acute intrabulbar injection of a low dose of AB (200 pmoles) on the OB local field potential before and during the presence of a hidden piece of smelly food. Our results show that AB decreases the power of OB network activity while impairs the animal´s ability to reach the hidden food. Moreover, we found a strong correlation between the power of the OB oscillations, as well as the correlation between the activities of both OBs, with the performance in the olfactory detection test. These findings provide a direct link between AB-induced OB network dysfunction and smell loss in rodents, which could be extrapolated to AD patients.

Disclosures: R.H. Soto: None. **K. Rojas Garcia:** None. **J. Peña Ortega:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.10/D27

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

Support: National Natural Science Foundation of China 81671248

Title: Retinal manifestations in mouse model of Alzheimer’s disease

Authors: *J. ZHANG, Y. SHEN;
Univ. of Sci. and Technol. of China, Hefei, China

Abstract: As an important component of the central nervous system, the visual system has driven an increased interest as a new research focus of Alzheimer's disease (AD). Studies in the visual system of AD patients have exhibited that they have worse complex visual functions such as contrast sensitivity, color vision, stereoacuity and visual acuity. The etiology of the visual impairment has been owing to the pathological changes of the visual cortex for a long time. Lately however, supported by modern ocular imaging techniques, it has been demonstrated that dysfunction of the anterior visual system also have an important impact on the development of visual symptoms in AD.
In the present study, we have utilized an array of molecular methods to examine retinal pathology in a well-characterized mouse models of AD(APP23). In our examination of existence of APP and deposits of amyloid plaques, the brains and retinas were collected from transgenic and wild-type mice of 3 to 12 months of age and processed for immunohistochemically analysis. In our results, human APP transgene were detected in several cell subtypes of retina and the APP expression were increased in transgenic mice compared with WT mice. In addition, deposits of Aβ were detected with immunostaining of whole-mount retinas. To our surprise, the deposits of retinal Aβ occurred earlier than that of the brain, indicating retinal pathologies may be among the earliest pathologies of AD. Furthermore, we found retinal neural degeneration in our APP23 mice. The distribution of cells in retinal ganglion cell layer of APP23 mice were sparser than that in WT mice and TUNEL-positive cells were detected in retinal ganglion cell layer in APP23 mice with TUNEL labeling. Moreover, activation of immune cells including microglia and astrocytes were not detected in retinas of APP23 mice, which were different from that in the brain.
The overall results of our research have demonstrated the retinal pathology of APP23 mice and provide a basis for future research of retinal pathology in AD.

Disclosures: **J. Zhang:** None. **Y. Shen:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.11/D28

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

Title: The effect of irrelevant visual experience on visual memory

Authors: S. INDULKAR, A. HOLT, S. FOWLER, ***J. SUBRAMANIAN**;
Univ. of Kansas, Lawrence, KS

Abstract: Long term memory storage involves increases in excitatory synaptic strength and connectivity between neurons encoding a novel experience. Such an increase in neuronal excitability would perturb neuronal firing rate homeostasis. Under conditions of neuronal

hyperactivity, such as in Alzheimer's disease, an increase in excitability induced by memory acquisition would further destabilize homeostasis. To identify whether excitability induced by task-irrelevant experience influences memory, we used a visual recognition memory (VRM) paradigm that involves synaptic plasticity in the primary visual cortex. In this paradigm, mice are repeatedly presented with a visual grating of a specific orientation and the recognition memory is assessed as a decrease in the exploration of the same stimulus over time. We tested the VRM in wild type mice and a mouse model of Alzheimer's disease (J20 line with human APP mutations) with or without task-irrelevant visual experience. We found that wild type mice display VRM for grating stimulus when tested one day but not at one month after the training period. In contrast, J20 mice did not exhibit VRM even one day after the training period. In the absence of task-irrelevant visual experience, J20 mice exhibited normal VRM and surprisingly, wild type mice did not. These results suggest that competing visual experiences improve visual memory in wild type mice but disrupt it under conditions of amyloid pathology.

Disclosures: S. Indulkar: None. **S. Fowler:** None. **J. Subramanian:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.12/D29

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

Title: Upregulation of MeCP2 level in red nucleus cause late-life depressive phenotypes

Authors: *Y. CHOI[1], J. RYU[2], H.-S. KIM[1], H.-I. IM[2];
[1]Seoul Natl. Univ. Col. Med., Seoul, Korea, Republic of; [2]Ctr. For Neurosci., Korea Inst. of Sci. & Technol., Seoul, Korea, Republic of

Abstract: Late-life depression affects 8 to 16% of older adults, and often co-occur with other neuropsychiatric disorders that many elderlies suffer from. To develop a protocol that selectively cause depression in old mice, we created a new stress schedule, and named our protocol the Social stress infused Unpredictable Chronic Mild Stress (SUCMS). Our study applied SUCMS to the C57BL/6J (B6) and C57BL/6 x C3H hybrid (B6/C3H) mice in young (2mo) and old age (7mo) to induce depressive-like state. The old B6 and B6/C3H mice, but not young B6 and B6/C3H mice, show increased lethargy when exposed to SUCMS. Interestingly, the old B6 and B6/C3H mice with SUCMS also exhibited cognition deficit. They also showed increased tendency of anxiety. For further study for other neuropsychiatric disorders related to late-life depression, we applied SUCMS in APP/PS1 transgenic mice. SUCMS exposed APP/PS1 transgenic mice showed increased tendency of lethargy, indicating that SUCMS can be also used for investigation of comorbidity study between depression and Alzheimer's disease (AD). Methyl CpG binding protein 2 (MeCP2) is a transcriptional regulator that involves in

maintaining synapses and normal function of cells that reside in the brain. A previous study revealed that elevated MeCP2 in mice causes cognitive deficits and Tau dysregulation. Therefore, we would like to confirm the expression level of MeCP2 in SUCMS exposed brain. They showed increased expression of MeCP2 in the red nucleus (RN), the brain region that is not much studied so far except for having functions of motor integration. Previous studies about RN have shown that activity of RN is related to upper limb tremor, reach-to-grasp movements and the reflex response. Also, a recent human brain imaging study proved significant connectivity between RN and the cerebral cortex. Although it is well known that cerebral cortex plays a key role in memory and perception, how RN affects cognitive function and depressive symptoms is not revealed. Our results indicate that induction of late-life depression results in overexpression of MeCP2 in RN, which eventually cause depressive behaviors, cognition decline and anxiety. We also expect that these pathological alterations in late-life depression affect the major symptoms of AD.

Disclosures: Y. Choi: None. **J. Ryu:** None. **H. Kim:** None. **H. Im:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.13/D30

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

Support: R15AG048447-01A1

Title: Age-related declines in short-term working memory, but not attention in APPswe/PS1dE9 transgenic mice

Authors: *P. L. SOTO[1], A. V. SAVONENKO[2], B. N. HARRIS[3];
[1]Dept. of Psychology, Louisiana State Univ., Baton Rouge, LA; [2]Pathology, Johns Hopkins Univ., Baltimore, MD; [3]Biol. Sci., Texas Tech. Univ., Lubbock, TX

Abstract: Alzheimer’s disease (AD) is a progressive neurological disease that results in cognitive deterioration, reduces quality of life, and is a significant economic burden on society. Currently available treatments for AD-associated cognitive impairment are minimally effective and can produce undesirable side effects. Thus, in the absence of a cure, there is a need for improved treatments for AD-associated cognitive impairment. The aim of the current study was to evaluate cognitive impairment in a mouse model of AD-associated beta amyloid neuropathology as a first step toward eventual screening of potential treatments. APPswe/PS1dE9 double transgenic male and female mice and non-transgenic littermates were trained on a delayed-matching-to-position (DMTP) or a 3-choice serial reaction time (3CSRT) task. Mice assigned to each task were further subdivided into two groups: (1) a continuous-

testing group, in which mice were exposed to daily experimental sessions five days a week from approximately 3-4 months of ages to 18 months of age and (2) an intermittent-testing group, in which mice were exposed to daily experimental sessions five days a week from approximately 3-4 months of age to 6 months of age, 10-12 months of age, and 16-18 months of age. Both transgenic and non-transgenic mice learned to perform the tasks quickly and with high levels of accuracy. Transient deficits in performance were observed following breaks in testing for both genotypes in both tasks. At 65 weeks of age, transgenic mice in the continuous-testing DMTP group exhibited increased rates of forgetting compared to non-transgenic mice but statistically significant deficits were not apparent in transgenic mice in the intermittent-testing DMTP group. The absence of deficits in transgenic mice in the intermittent-testing DMTP group appears to be due increased forgetting in the non-transgenic mice relative to rates of forgetting in the continuous-testing non-transgenic mice. In comparison, deficits were not apparent in transgenic mice in the 3CSRT task in either the continuous- or intermittent-testing groups. The results demonstrate a selective decline in short-term working memory in APPswe/PS1dE9 mice and indicate that intermittent testing obscures the development of deficits by impairing performance in non-transgenic mice. Future studies evaluating potential experimental treatments (e.g., potential pharmacotherapeutics) in APPswe/PS1dE9 mice can use a continuous-testing DMTP procedure to evaluate the ability of experimental treatments to alleviate or prevent declines in short-term working memory due to Alzheimer's disease-related amyloidosis.

Disclosures: P.L. Soto: None. **A.V. Savonenko:** None. **B.N. Harris:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.14/D31

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

Title: Automated cognitive testing in mouse models relevant to Alzheimer's disease

Authors: *B. KOOPMANS, M. E. SCHOENBERG, M. LOOS;
Sylics, Amsterdam, Netherlands

Abstract: Working memory impairments are observed in a variety of neurological and psychiatric diseases, including Alzheimer's disease (AD) and Schizophrenia. Working memory performance relies on a set of cognitive processes including retrieval of information from short-term hippocampal-based memory storage as well as manipulation of online information by prefrontal executive functions. In order to develop promising interventions to counteract deficits underlying cognitive systems it is key to develop robust preclinical tests in mice that can assess these cognitive functions. However, current working memory tasks for rodents require extensive training, as well as frequent human intervention. Therefore, we aimed to developed an

automated, home-cage (PhenoTyper™) based task to measure working memory deficits in AD and Schizophrenia mouse models using a modified version of the traditional eight-arm radial maze and 24/7 video tracking software. We previously described an automated one-night CognitionWall task that may be used to measure discrimination learning, but that cannot be used to specifically dissect working memory from short-term memory performance. We investigated the effect of a systemic injection of a low-dose, non-competitive NMDAr antagonist (MK-801) on performance in the task, as well as performance of transgenic APP/PS1 mice that showed impairments in the one-night CognitionWall task. The novel working memory tasks allows separate analyses of working memory and reference memory errors. Due to the significant reduction in both training time and human intervention, this PhenoTyper™-based task may prove instrumental in preclinical testing of interventions targeting AD and other cognitive disorders.

Disclosures: **B. Koopmans:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV). **M.E. Schoenberg:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV). **M. Loos:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV).

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.15/D32

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

Support: Alzheimer's Association Grant # 2016-MNIRGD-391961
Nova Scotia Research and Innovation Trust Grant # 34123

Title: Social interest in 5xFAD mice is influenced by genotype of social stimuli

Authors: *F. KOSEL, J. K. GLIKLICH, T. B. FRANKLIN;
Psychology and Neurosci., Dalhousie Univ., Halifax, NS, Canada

Abstract: In addition to cognitive impairments, patients with Alzheimer’s disease (AD) exhibit a number of behavioural and psychological symptoms of dementia (BPSD), with apathy (including social withdrawal) being the most prevalent. We have previously found that the 5xFAD transgenic mouse model of AD can be used to model some of these BPSD, with transgenic females exhibiting an age-related decrease in social investigation from 3 to 12 months of age. The present study examines whether this decrease in social investigation is affected by the genotype of the stimulus conspecific, and whether transgenic 5xFAD males exhibit similar reductions in social investigation. Social approach behaviour in female and male transgenic 5xFAD mice and wild-type controls at 6 months of age was examined using a modified Y-maze apparatus. Preliminary results indicate that transgenic 5xFAD mice exhibit reduced social approach behaviour compared to wild-type controls, and that social approach behaviour is

influenced by the genotype of the conspecific. This research suggests that both female and male transgenic 5xFAD mice model the reduced social interest exhibited by AD patients, and that interactions between individuals carrying AD genotypes can lead to heightened dysfunction in social relationships.

Disclosures: **F. Kosel:** None. **J.K. Gliklich:** None. **T.B. Franklin:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.16/D33

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

Support: Grant 81770839
Grant 81571125
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Grant 91132712
Grant 81300979
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Grant 81521062

Title: Amyloid β oligomers suppress excitatory transmitter release via presynaptic depletion of phosphatidylinositol-4,5-bisphosphate

Authors: *X. MA, Y. HE, M. WEI, Y. ZHOU, Y. SHEN;
Zhejiang Univ., Hangzhou, China

Abstract: Amyloid β (Aβ) oligomer-induced aberrant neurotransmitter release is proposed to be a crucial early event leading to synapse dysfunction in Alzheimer’s disease (AD). In the present study, we report that the release probability (Pr) at the synapse between the Schaffer collateral (SC) and CA1 pyramidal neurons is significantly reduced at an early stage in mouse models of AD with elevated Aβ production. High nanomolar synthetic oligomeric $A\beta_{42}$ also suppresses Pr at the SC-CA1 synapse in wild-type mice. This Aβ-induced suppression of Pr is mainly due to an mGluR5-mediated depletion of phosphatidylinositol-4,5-bisphosphate(PIP2) in axons. Selectively inhibiting Aβ-induced PIP2 hydrolysis in the CA3 region of the hippocampus strongly prevents oligomeric Aβ-induced suppression of Pr at the SC-CA1 synapse and rescues synaptic and spatial learning and memory deficits in APP/PS1 mice. These results first reveal the presynaptic mGluR5-PIP2 pathway whereby oligomeric Aβ induces early synaptic deficits in AD.
Keywords: mGluR5; Release Probability; Oligomeric Aβ; Phosphatidylinositol-4,5-bisphosphate; Presynaptic; Alzheimer's Diseas

Disclosures: **X. Ma:** None. **Y. He:** None. **M. Wei:** None. **Y. Zhou:** None. **Y. Shen:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.17/D34

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

Support: RO1AG058171
NIH T32 AG057461

Title: Neuronal calcium homeostasis in dorsal hippocampus in the HNE and 5xFAD mouse models of Alzheimer's disease across age

Authors: *A. O. GHOWERI[1], L. J. OUILLETTE[2], H. N. FRAZIER[1], A. ELHARRAM[5], K. L. ANDERSON[1], R. PARENT[3], J. C. GANT[1], B. BENNETT[6], G. G. MURPHY[4], O. THIBAULT[1]; [1]Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY; [3]Mol. and Behavioral Neurosciences Inst., [4]MBNI/Physiology, [2]Univ. of Michigan, Ann Arbor, MI; [5]Pharmacol. and Toxicology, [6]Biomed. and Mol. Sci. and Ctr. for Neurosci. Studies, Queen's Univ., Kingston, ON, Canada

Abstract: With limited treatment options and no known cure, the need to develop novel therapeutics based on underlying cellular mechanisms in aging and Alzheimer’s disease remains imperative. Over the past few decades, a constellation of neuronal phenotypes associated with AD and aging have been extensively studied in animal studies. One potential mechanism highlighted in the calcium hypothesis of brain aging and dementia describes dysregulation of neuronal calcium that impacts cellular physiology and synaptic connectivity. Prior work has described an increase in the Ca2+-dependent afterhyperpolarization (AHP), associated in a few studies, with an increase in intracellular calcium levels. This association has become recognized as a reliable biomarker of normal aging; specifically seen in pyramidal neurons of hippocampal field CA1. Despite this, less is known about the relationship between the AHP and neuronal calcium handling in AD models. In fact, recent work has shown that a reduction in L-type voltage sensitive calcium channels (L-VSCCs) were present in aged APP and PS-1 AD mouse models. This suggests calcium dysregulation in AD models may differ from normal aging; perhaps influencing disease progression.
In this study, we measured the AHP and intracellular calcium across age in the HNE and 5xFAD AD mouse models. The HNE mouse is an oxidative stress-based model of sporadic AD based on gene deletion of aldehyde dehydrogenase 2, resulting in elevated levels of the lipid peroxidation product, 4 hydroxynonenal (HNE). Animals were studied at 1.5, 4, and 10 months of age following along the development of AD pathology (i.e. Abeta). Sharp electrode electrophysiology was used to measure AHPs in neurons of the *stratum pyramidale* in field CA1

of the dorsal hippocampus, and changes in calcium during synaptic activation were quantified using the fluorescent indicator OGB-1. By 4 months, a trend of an attenuated AHP was observed in the 5xFAD animals compared to their wildtype counterparts. However, at this age, 5xFAD mice do not show behavioral deficits in the Morris Water Maze task of spatial reference memory. Interestingly, whereas HNE mice do show memory deficits at 4 months of age, no alterations in the AHP were observed. Preliminary data on the 10-month 5xFAD mice illustrate further reductions of the AHP and intracellular calcium. Thus far, these data corroborate our previous findings of reduced L-VSCCs in AD mouse models and suggest that decreases in somatic calcium may be a precipitating factor in downstream behavior deficits but only in one animal model of AD. These reductions in calcium handling may increase synaptic excitability and stimulate the onset of cognitive decline.

Disclosures: A.O. Ghoweri: None. **L.J. Ouillette:** None. **H.N. Frazier:** None. **A. Elharram:** None. **K.L. Anderson:** None. **R. Parent:** None. **J.C. Gant:** None. **B. Bennett:** None. **G.G. Murphy:** None. **O. Thibault:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.18/D35

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

Title: The histological and biochemical effects of A. bisporus (white button mushrooms) on human amyloid precursor protein (hAPP) transgenic mice

Authors: *T. T. DIMOPOULOS, K. M. CRAVEN, R. E. BARKEY, E. N. DOHERTY, C. M. HERNANDEZ, J. M. FLINN;
George Mason Univ., Fairfax, VA

Abstract: Alzheimer’s Disease (AD) affects 5.7 million Americans. White button mushrooms (WBMs) are considered an antioxidant due to their high source of selenium and have been shown to promote nerve growth factors (NGFs), as well as slow cognitive decline in AD. Selenoproteins, particularly Selenoproteins M (SelM) and P (SelP), are an integral part of memory consolidation and preservation in mouse models.
J20/hAPP transgenic mice and wildtype (C57BL/6J) mice from Jackson Laboratories were fed a 10% WBM feed three times per week to yield a 5% total diet of WBMs. Behavioral tests were conducted at 3.5 months and 8 months of age. Interestingly, at 3.5 months J20 mice on the WBM diet had increased latency in Morris Water Maze (MWM) compared to J20 mice on the control diet ($p<0.001$). In contrast, at 8 months, J20 mice on the WBM diet had faster latency ($p<0.005$) in MWM than J20s not on the diet; thus, an ameliorative effect of the WBM diet on spatial memory is evident in these older animals. Preliminary Congo Red staining for Aβ plaques show

increased plaque load at 8 months in J20 mice on the WBM diet, compared to J20 mice not on the WBM diet, in the CA2 and CA3 regions of the hippocampus and corpus callosum. Western Blot and immunohistochemistry (IHC) will determine whether the WBM diet affects SelM, SelP, NGF, and total APP concentration.

Disclosures: T.T. Dimopoulos: None. **K.M. Craven:** None. **R.E. Barkey:** None. **E.N. Doherty:** None. **C.M. Hernandez:** None. **J.M. Flinn:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.19/D36

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

Support: NIH/NIA R01 AG040178
NIH/NIA T32 AG000213-27

Title: The amyloid plaque microenvironment

Authors: *D. C. SOUDER[1], I. A. DREISCHMEIER[2], S. L. WRIGHT[2], K. W. ELICEIRI[3], R. ANDERSON[2];
[1]Dept. of Geriatrics and Gerontology, [3]Lab. for Optical and Computat. Instrumentation, [2]Univ. of Wisconsin-Madison, Madison, WI

Abstract: Background: Amyloid plaque formation is a central event in Alzheimer’s disease (AD) pathology. Our current understanding of plaque formation, clearance, and impact on the surrounding tissue is largely based on mouse models of amyloidosis; however, sporadic AD includes age as a major risk factor and many aspects of AD pathology appear to be specific to humans. Here we utilize APP/PS1 mice, a genetic model of AD, rhesus monkeys that spontaneously develop amyloid plaques with age, and human AD brain tissue to determine if features of the amyloid plaque microenvironment are conserved from mice to humans. **Methods:** Brain tissue was obtained from six-month-old APP/PS1 male mice (n=6), from 28-34 year old male and female rhesus monkeys from the Wisconsin National Primate Research Center longitudinal study on aging (n=7), and from male and female individuals with confirmed AD diagnosis whose brain tissue was banked at the Wisconsin Brain Donor Program (n=14). For each species, tissue sections of the medial temporal cortex were used for histochemistry, immunofluorescence, and 2-photon microscopy. **Results:** Amyloid plaques were associated with astrogliosis, elevated mitochondrial density, and increased cytochrome c oxidase activity. The total area affected by reactive astrocytes was greater in monkeys and humans than in mice; however, mice displayed more robust increase in GFAP expression in the plaque vicinity. We report that plaques induce a unique metabolic signature that is conserved between species.

Furthermore, areas of elevated NAD(P)H fluorescence correlate with high mitochondrial density. These results suggest that functionally distinct mitochondria exist within and around amyloid plaques. **Conclusion:** Our data suggests that mitochondrial dysfunction is a key aspect of AD pathology. Mitochondrial localization, function, and NAD(P)H cofactor status are altered in proximity to amyloid plaques. Importantly, transgenic models of AD fail to capture heterogeneity in the metabolic environment around spontaneously formed plaques, indicating that nonhuman primates may be a better model for understanding the proximal consequence of AD pathology.

Disclosures: D.C. Souder: None. **I.A. Dreischmeier:** None. **S.L. Wright:** None. **K.W. Eliceiri:** None. **R. Anderson:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.20/D37

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

Support: Alzheimer's Society of Alberta and North West Territories
Alberta Prion Research Institute

Title: Seeding of a fast-acting Abeta peptide accelerates plaque deposition and microgliosis in APP^{NL-G-F} mouse model with no impairment in learning and memory

Authors: *S. G. LACOURSIERE[1], M. H. MOHAJERANI[1], D. A. WESTAWAY[2], R. J. SUTHERLAND[1];
[1]Canadian Ctr. For Behavioural Neurosci., Lethbridge, AB, Canada; [2]Univ. of Alberta, Edmonton, AB, Canada

Abstract: Alzheimer’s disease (AD) is characterized by a stereotypical conformational misfolding of certain brain proteins. Of specific interest is amyloid-β (Aβ) due to its prion-like properties. However, the role of Aβ in AD symptoms remains unclear. It has been hypothesized that the emergence of Aβ plaque impairs cognition and therefore accelerating Aβ pathology should increase the severity of cognitive symptoms. The medial entorhinal cortex of the KI-APP^{NL-G-F}. mouse model, both homozygous positive ($APP^{+/+}$) and negative ($APP^{-/-}$) were seeded with brain homogenates containing fast-acting (FA) or control (C) at 2 months of age. At 3 (n = 14), 4.5 (n = 12), and 6 (n = 8) months of age, learning and memory were tested using the Morris water task (MWT). Groups were randomized with $APP^{+/+}$ and $APP^{-/-}$ with either FA or C injections housed in the same cages; the experimenter was blinded to the experimental manipulation during testing. Immunohistochemical staining showed dramatically increased 82E1 and Iba1 labelling, indicating increased Aβ and microgliosis pathology, respectively, in the

$APP^{+/+}$ FA mice as early as 3 months of age. In the no-platform probe of the Morris Water Task at 6 months, the $APP^{+/+}$ FA mice spent similar time (59.7 ± 8.35%) compared to the non-seeded controls (73.0 ± 2.00; results presented as mean ± SEM); showing no association between Aβ plaque pathology and learning and memory ability. Our results replicate previous reports of the seeding properties of Aβ and its prion-like behaviour (Kane, M.D. et al., 2000). We have also shown that the Aβ seed used spreads rapidly, much faster than we predicted by transneuronal spread; this is either a testament to the seeding ability of specific strains of Aβ or provides evidence against the transneuronal spread of Aβ. Furthermore, our results show that Aβ plaque is not directly the causal agent for memory impairment.

Disclosures: **S.G. Lacoursiere:** A. Employment/Salary (full or part-time):; University of Lethbridge. **R.J. Sutherland:** A. Employment/Salary (full or part-time):; University of Lethbridge. **M.H. Mohajerani:** A. Employment/Salary (full or part-time):; University of Lethbridge. **D.A. Westaway:** A. Employment/Salary (full or part-time):; University of Alberta.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.21/D38

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

Support: Alzheimer's Association Research Award to Promote Diversity
Emory University Alzheimer's Disease Research Center Pilot Grant

Title: Determining therapeutic amyloid beta reduction necessary for improved cognition in Alzheimer’s mice

Authors: M. C. MAKER[1], J. PRAKASH[2], *C. S. MITCHELL[2];
[1]Columbia Univ., New York, NY; [2]Georgia Inst. of Technol., Atlanta, GA

Abstract: Beta-secretase cleaving enzyme (BACE) is an enzyme encoded by the BACE1 gene that assists in the division of the amyloid-precursor protein (APP). Currently, BACE (beta-secretase cleaving enzyme) inhibitors are being tested for clinical use in familial Alzheimer’s disease (AD) as a possible preventative treatment to prevent or decrease amyloid beta buildup. However, multiple studies have failed to emphasize the extent by which amyloid beta needs to be reduced before improvements to cognition are observed. The goal of this study is to quantify the amyloid beta reductions necessary for significantly improved cognition in transgenic AD mice. A meta-analysis was performed using PubMed keywords “Alzheimer’s disease, amyloid-beta, beta-secretase, and Morris Water Maze”. Ultimately, 23 papers matched inclusion criteria. Escape latency of Morris Water Maze, both the insoluble and soluble 40/42 amyloid beta levels, and the BACE levels were extracted from the papers using WebPlot Digitizer. Descriptive,

exploratory, and predictive analysis are performed on aggregated data. When comparing amyloid beta 42 to escape latency, clustering showed a 25 point decrease in amyloid beta led to a 10 point decrease in escape latency while a 40 point decrease in amyloid beta led to a 20 point decrease in escape latency over the AD model. For reference, Wild-type (WT) mice have an escape latency 25 points lower than the AD model. This exploratory assessment will be further assessed with more explicit analytical methods to predict what treatment effect size is needed from BACE inhibitors for amyloid beta reduction that results in a significant impact on cognition. Results demonstrate amyloid beta needs to be greatly reduced, about 40 points, in order to achieve WT levels of cognition. This same group needed to achieve a BACE decrease of 40 points to achieve these levels of amyloid beta. These findings serve to conclude that BACE inhibitors could have a significant effect on the cognitive decline of patients with either familial or sporadic AD, but require a tremendous amount of amyloid beta and BACE reduction to achieve it.

Disclosures: M.C. Maker: None. **J. Prakash:** None. **C.S. Mitchell:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.22/D39

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

Title: Disease progression characterization of a new model for Alzheimer's disease

Authors: *X. CHENG[1], L. ZHUANG[1], Z.-Q. XIONG[2];
[1]Inst. of Neuroscience, Chinese Acad. of Sci., Shanghai, China; [2]Inst. Neurosci, Shanghai, China

Abstract: Alzheimer’s disease (AD), with a 10% prevalence in people with age beyond 65, has clinical manifested symptoms mainly including cognitive dysfunctions and neuropsychiatric impairments. Modeling of AD with *C. elegans*, flies and rodents has greatly promoted our understanding of molecular and cellular mechanisms of diseases. However, due to their differential genetics, metabolism, distinctive architecture and circuit connections from humans, these models often could not fully simulate human diseases. Thus, therapeutic trials developed based on them came out with an extremely high failure to work on human patients. Several β amyloid-targeting therapies, including vaccines, antibodies, and inhibitors or modulators of γ- and β-secretase are currently being tested. Although current drug pipeline in clinical trials contains a cohort of potential disease-modifying drugs, a long list of failures of AD clinical trials in recent years has casted a long shadow on the future of AD drug development. It implies that our current theories and mechanistic understanding of AD pathogenesis obtained largely by using rodent models may be incomplete or incorrect. Being phylogenetically and structurally more closer, non-human primates (NHPs) may be a better choice of disease model system to fill the long-lasting gaps at mesoscopic and microscopic level. In the past decades, stereotaxic

injection of the cytotoxin ibotenic acid into the basal forebrain or transection of the fornix of macaque monkeys were used to mimic the loss of cholinergic basal forebrain neurons and associated cognitive deficits. Moreover, intracerebral delivery of ß-amyloid plaques and neurofibrillary tangles has also been used to induce AD-like symptoms in monkeys. However, a lack of genetically-modified AD model has been impeding AD research. We are trying to establish a transgenic macaque model that mimicking both the copy-number duplication/triplication and point-mutation of APP and PSEN1 gene. The disease progression of transgenic monkeys will be characterized by using combined strategies including plasma/CSF biomarker identification, PET imaging and cognitive function behavioral analysis. We hope this would be a valuable model to facilitate AD research.

Disclosures: X. Cheng: None. **L. Zhuang:** None. **Z. Xiong:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.23/D40

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

Support: Alzheimer's Association SAGA Grant
NIH AG05681
NIH NS074969

Title: Signaling pathways involved in the differential stress response on Aβ levels in male and female mice

Authors: C. M. YUEDE[1], C. E. WALLACE[2], W. D. GARDINER[3], H. L. RIDENBARK[4], T. DAVIS[5], ***J. R. CIRRITO**[6];
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Abstract: Results from both human and animal studies over the last decade have identified a clear increase in the rate of Alzheimer’s disease (AD) in women. Sex differences in the prevalence or severity of many diseases are well recognized. A common underlying feature of disorders more prevalent in females is an association with stress, such as in anxiety and depression. Stress increases glucocorticoids (GC) in the brain, and the link between GCs and AD has been confirmed by several studies. Differences between males and females in corticotropin releasing factor (CRF) receptors, particularly in the locus coeruleus, have been described extensively by Bangasser and colleagues (2011, 2013, 2018). We previously found that acute stress rapidly increases levels of Aβ in the mouse brain (Kang et al., 2007), and that this effect

was dependent on synaptic activity and CRF. The influence of specific CRF or glucocorticoid signaling pathways on AD pathology has not been defined. Here we manipulate signaling molecules involved in the CRF receptor pathway to determine the mechanisms underlying to sex-related differences in Aβ levels in response to acute stress. Using microdialysis, Aβ levels in the interstitial fluid (ISF) of the hippocampus were measured in male and female APP/PS1 mice (3-4 months old). Samples were collected every hour for a baseline period, 3-hour restraint stress, and 12-hour post stress period. Activators and inhibitors of PKA were administered for 6 hours prior to acute stress to determine the influence of these signaling pathways on acute stress-induced increases in Aβ levels. The increase in Aβ in response to acute stress is a predominantly female response showing a significant difference between male and female mice in the percent increase in ISF Aβ during acute stress, with female mice having a much greater and sustained increase in ISF Aβ compared to males. Inhibiting PKA prior to acute stress completely blocked the stress-induced increase in ISF Aβ levels in female APP mice. Activating PKA in males resulted in a delayed increase in ISF Aβ following acute stress that was not seen in vehicle treated mice. These results suggest that females are more sensitive to stress-induced increases in Aβ, and that acute stress increases Aβ in female mice through stress-induced PKA signaling.

Disclosures: J.R. Cirrito: None. **C.M. Yuede:** None. **C.E. Wallace:** None. **H.L. Ridenbark:** None. **T. Davis:** None. **W.D. Gardiner:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.24/D41

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

Support: Mechanisms of Aging and Dementia Training Grant AG020506
NIH Grant AG017139

Title: Myelination changes in hippocampal white matter during Alzheimer's pathogenesis and the electrophysiological consequences

Authors: *M. L. RUSSO, T. F. MUSIAL, G. D. AYALA, S. J. AHMAD, L. A. BEAN, D. A. NICHOLSON;
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Abstract: Recent work employing diffusion tensor imaging (DTI) has implicated white matter deterioration as a potential predictive biomarker for Alzheimer’s disease (AD). However, few studies have utilized high resolution techniques to understand the tissue-level changes that underlie white matter disruption observed with DTI. Fortunately, *in vitro* experiments and histological examinations of the grey matter have provided some insight into potential

explanations for this phenomenon. Specifically, oligodendrocytes, the myelinating glial cells that are abundant in the white matter, exhibit susceptibility to amyloid beta toxicity in culture. Moreover, light and fluorescence microscopy have consistently shown decreased myelination in and around the cores of amyloid plaques. Such observations suggest that detrimental effects of AD pathology to oligodendrocytes and subsequent changes to myelination may play a role in white matter deterioration. Therefore, we used a combination of morphological and functional experiments to assess how myelin deficits contribute to white matter disruption in AD. First, using conventional electron microscopy we quantified instances of abnormal myelination within the alveus of 5xFAD mice, post-mortem human AD tissue, and corresponding controls. This analysis revealed that aged 5xFAD mice exhibit significantly more instances of abnormal myelination than age-matched controls, as well as all mice classified as young adult or middle aged. Human AD tissue exhibited a similar trend relative to tissue from non-cognitively impaired individuals. Second, whole-cell current clamp was utilized to assess the physiological consequences of myelin disruption in AD mouse models. In the experimental setup, antidromic action potentials (aAP) were initiated by a stimulating electrode placed in the alveus of CA1, and aAP propagation to the soma was monitored by a somatic recording electrode. Statistical analysis revealed a main effect of genotype on successful aAP propagation, such that neurons from 5xFAD mice exhibit lower rates of successful propagation. This data suggests that white matter deterioration observed by DTI in AD patients may be the result of dysmyelination. Further, our findings indicate that myelination changes result in electrophysiological consequences that likely contribute to disrupted neuronal communication during AD.

Disclosures: **M.L. Russo:** None. **T.F. Musial:** None. **G.D. Ayala:** None. **S.J. Ahmad:** None. **L.A. Bean:** None. **D.A. Nicholson:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.25/D42

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

Support: NIH R01 NS086965
NIH R01 NS085171

Title: Distinct gene expression patterns in the dentate gyrus of Alzheimer’s disease mice with differential susceptibility to spontaneous seizures and memory loss

Authors: *C.-H. FU[1], X. ZHANG[2], G. S. STEPHENS[1], Y. LIU[3], J. CHIN[1];
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Abstract: Alzheimer's disease (AD) is characterized by amyloid plaques and neurofibrillary tangles, but not all individuals with neuropathology are cognitively impaired. Why some individuals appear resistant to cognitive decline is unclear. Using human amyloid precursor protein (APP) transgenic mice, we found that a proportion of APP mice do not exhibit memory deficits even though they produce similar levels of amyloid-beta (Aβ) as other APP mice that do exhibit memory deficits. Interestingly, memory deficits correlated with spontaneous seizure activity; APP mice with frequent seizures had poor memory, and APP mice that did not have seizures had normal memory. Patients with mild cognitive impairment or AD also have increased incidence of seizures, which predict faster and more severe cognitive decline. To investigate why some APP mice have frequent seizures and cognitive impairment while others do not, we stratified APP mice based on dentate gyrus expression of ΔFosB, a transcription factor whose expression we previously found highly correlates with seizure frequency. We performed RNA-sequencing on dentate gyrus from nontransgenic (NTG) control mice, APP mice with high ΔFosB levels ("APP-high"), and APP mice with control levels of ΔFosB similar to NTG mice ("APP-ctrl"). Of the three groups, APP-high mice differed the most in gene expression patterns compared with NTG mice and APP-ctrl mice. Gene clustering analyses revealed that the expression differences between APP-high mice and NTG or APP-ctrl mice involved many ion channels and excitability-related genes. Surprisingly, despite having similarly high levels of APP/Aβ, APP-ctrl mice had gene expression profiles largely different from that of APP-high mice, but very similar to that of NTG mice. These results suggest that APP-ctrl mice are similar to NTG mice in terms of memory, lack of seizures, and gene expression patterns. Notably, a small set of genes were differentially expressed in APP-ctrl mice compared with either NTG or APP-high mice, suggesting they may play a role in conferring resistance to the effects of Aβ and/or seizures. Understanding how these varying patterns of gene expression arise may provide insight into mechanisms that underlie differential susceptibility to cognitive deficits in AD.

Disclosures: C. Fu: None. **X. Zhang:** None. **G.S. Stephens:** None. **Y. Liu:** None. **J. Chin:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.26/D43

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

Support: NIH Grant 800105

Title: Role of Tip60 in the nuclear and cytoplasmic proteome of amyloid precursor protein-induced neurodegenerative condition

Authors: *B. KARISETTY[1], F. ELEFANT[2];
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Abstract: Alzheimer's disease (AD) has been shown by our group and others to be is associated with epigenetic dysregulation. Histone acetylation, an important epigenetic regulator, is maintained by opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Our lab has shown a reduction in the total and neuronal nuclei Tip60 (HAT) levels in human AD hippocampus. We further showed that external stimulation of hippocampal neuronal cells increases Tip60 nuclear import and enhances transcription of target genes. Also, cytoplasmic Tip60 can acetylate microtubules associated with neuronal function. A study suggests that Amyloid Precursor Protein (APP) may participate in Tip60 nucleocytoplasmic shuttling by membrane sequestration, phosphorylation and nuclear import. Notably, shuttling process regulates protein activity and is a common theme in multiple neurodegenerative disorders. Here we used transgenic AD-associated *Drosophila* expressing human APP 695 isoform and double transgenic flies (APP; Tip60) expressing APP with increased Tip60 levels in the brain to explore a role for Tip60 in nucleocytoplasmic shuttling in AD. 1-2-day old adult heads were used for molecular work. mRNA levels of individual (A & B) and total transcript variants (A, B & C) of Tip60 were measured. Interestingly, transcript variant specific regulation (A) was observed in the APP fly line. At the protein level, nuclear and cytoplasmic protein fractions isolated from APP and APP; Tip60 fly heads were used for label-free quantitative proteomics to measure the differential regulated proteins and the nuclear or cytoplasmic enrichment of proteins. We identified many differentially regulated proteins in the APP line with a good number of these respective proteins being restored in the APP; Tip60 line. Proteins involved in pathways like Apo-B biosynthesis and splicing were specifically altered in the nucleus and proteasome and ubiquitin pathways in the cytoplasm. We also observed nuclear enrichment of multiple proteins in APP line and decrease of these respective protein levels in the APP; Tip60 line. These results suggest transcript variant specific regulation of Tip60 and nuclear/cytoplasmic protein enrichment regulation by overexpressed Tip60 in APP-induced neurodegeneration.

Disclosures: B. Karisetty: None. **F. Elefant:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.27/D44

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

Support: Alzheimer's Association New Investigator Research Grant: NIRG-12-241456
National Institute on Aging: 1K01AG42500

Delaware IDeA Network of Biomedical Research Excellence (INBRE) Pilot Award: NIH-NIGMS
NIH-NIGMS Center of Biomedical Research Excellence (COBRE): 5P20GM103653
NSF: 1728804
Delaware Economic Development Office Grant from the State of Delaware

Title: Selective TDP-43 expression in an aged APP/PSEN1 background

Authors: *A. ANDERSON, S. DAVIS, K. WILSON, M. GITCHO;
Biol. Sci., Delaware State Univ., Dover, DE

Abstract: TDP-43 functions as a heterogeneous nuclear ribonucleoprotein involved in mRNA transport, mRNA stability, transcription, mitochondrial metabolism, and forms stress granules in the cytosol. TDP-43 is the major pathological protein in frontotemporal dementia and ALS. Previously, TDP-43 pathology has been described in up to 50% of those with Alzheimer's disease. Recent evaluation of this cohort revealed a distinct pathological staging of TDP-43 proteinopathy in an aged population, which overlaps frontotemporal lobar degeneration (FTLD-TDP) and Alzheimer's disease. This overlapping pathological cohort is named limbic-predominant age-related TDP-43 encephalopathy (LATE). Through a model of cortical/hippocampal expression in an APP/PSEN1, we have extended our previously reported characterization of 9-month old mice to determine how age contributes to neurodegeneration. This TDP-43 proteinopathy is present in 20-50% of LATE cases in those 80 and over. The mice characterized for this study are 24 months of age, which may be comparable to approximately 70 years of age in humans. Both human TDP-43 and nuclear localization signal defective (ΔNLS) TDP-43 in an APP/PSEN1 background were evaluated. This model shows severe neuronal loss in the hippocampus, a change in plaque deposition, aggregated tau, and a decrease in survival. This aged model of TDP-43 proteinopathy may be of use in understanding how TDP-43 contributes to neurodegeneration.

Disclosures: **A. Anderson:** None. **S. Davis:** None. **K. Wilson:** None. **M. Gitcho:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.28/D45

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

Support: R37-AA014983-13S
P60-AA011605

Title: Accelerated expression of amyloid-beta biomarkers and behavioral pathologies after moderate alcohol drinking in a humanized triple transgenic mouse model of Alzheimer's disease

Authors: *J. L. HOFFMAN[1], S. P. FACCIDOMO[2], S. M. TAYLOR[1], M. KIM[1], C. W. HODGE[3];
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Abstract: ***Rationale:*** Alzheimer's disease (AD) is a progressive neurodegenerative disorder, representing the most common cause of dementia in the USA. Elderly populations are consuming more alcohol than prior generations and preclinical research is needed to fully elucidate neurobiological mechanisms that underlie the interaction between AD and alcohol use. We have evaluated the impact of alcohol drinking on the prefrontal cortex and amygdala neuroproteome and bioinformatics revealed a striking association between alcohol drinking and AD pathology. In both regions, the AD-linked proteins tau, amyloid-β (Aβ) precursor protein, and presenilin-1 were identified as the main modulators of alcohol-sensitive protein networks, suggesting that alcohol drinking may alter the course of AD pathology. ***Objective:*** To investigate the effects of chronic alcohol drinking pathologies associated with AD in a triple-transgenic mouse model of AD(3xTg-AD mouse) that expresses human tau, amyloid precursor protein and presenilin-1 genes. ***Methods:*** Male and female 3xTg-AD and control mice (B6129SF2J) were given 24-h access to 25% alcohol/0.1% saccharin+water or 0.1% saccharin+water beginning at 3-mo of age. Mice were tested for behavioral impairments periodically between 40-day bouts of 24-h access alcohol consumption. At approximately 7-mo old and after a final bout of homecage drinking, behavioral impairments were assessed in the open-field, Morris water maze and acoustic startle chamber. Mice were then euthanized and brains were removed for analysis of early-disease biomarkers Aβ40 and Aβ42. ***Results:*** Both genotypes consumed similar amounts of saccharin and alcohol at all time points and behavioral differences emerged at 7-mos. As expected, impaired spatial learning developed in the 3xTg-AD mice; though, alcohol drinking did not exacerbate this deficit. A notable impairment was found in pre-pulse inhibition (PPI) of the startle response for 3xTg-AD alcohol drinking mice as compared to all other groups. These behavioral changes were accompanied by significant increases in Aβ42/Aβ40 ratio in the cortex (CTX) and lateral entorhinal cortex (l-ENT). ***Conclusions:*** Early indicators of learning and memory impairments in the 3xTg-AD mice were not altered by alcohol drinking. However, initial data indicate impaired sensorimotor gating, a common symptom of AD, in the 3xTg-AD alcohol drinking mice. Together with the increased neuropathology the l-ENT and CTX after alcohol drinking, these data support the hypothesis that moderate alcohol drinking may accelerate the onset of AD pathology and may be an important risk factor for the development of AD.

Disclosures: J.L. Hoffman: None. **S.P. Faccidomo:** None. **S.M. Taylor:** None. **M. Kim:** None. **C.W. Hodge:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.29/D46

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

Title: Target validation for Alzheimer's disease using multiplex RNAscope technology

Authors: *K. T. KAYE, N. RUDERISCH, J. PIRO, T. DELLOVADE;
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Abstract: Alzheimer’s disease is the most common form of dementia that leads to severe memory loss and cognitive decline, affecting millions of patients and families worldwide. To understand the gene expression changes of aging in the brain, we explore the value of using *in situ* hybridization (ISH) to detect specific target RNA such as APOE. Advanced Cell Diagnostic’s (ACD) Multiplex RNAscope is an automated ISH assay that enables single-molecule detection of multiple RNA targets simultaneously. Using ACD’s Tyramide Signal Amplification probe technology, this assay is designed to significantly boost signal while suppressing background noise. Advantages of this assay include easy-to-use automated technology, strong detection of low expressing genes in any channel, dual ISH and immunohistochemistry (IHC), and compatibility across various tissue samples. High expressing genes such as APOE and TFR were used to validate dual ISH and IHC, which showed exceptional signal across mouse models. Low expressing targets provided challenges in aged tissue due to existing pathology. Despite these challenges, RNAscope technology provides a clear visualization of gene expression changes in aging rodent models, which will help us understand the aging mechanisms in Alzheimer’s patients and select meaningful therapeutic targets.

Disclosures: **K.T. Kaye:** None. **N. Ruderisch:** None. **J. Piro:** None. **T. Dellovade:** None.

Poster

471. Alzheimer's Disease: APP/Abeta Animal Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 471.30/E1

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

Support: DP2EB028110

Title: Probing the role of exosomes derived from peripheral organs and tissues in the onset and progression of Alzheimer's disease

Authors: *W. LAWRENCE[1], D. F. ALZATE-CORREA[3], J. T. MOORE[4], C. L. RINK[5], N. HIGUITA-CASTRO[2], D. GALLEGO-PEREZ[2];
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Abstract: Alterations in the levels of amyloid beta and phosphorylated tau have been previously documented in non-neural tissues and blood of Alzheimer's disease (AD) patients, however the potential relation of these findings to the onset and progression of AD remains to be elucidated. Furthermore, while neuron-derived exosomes have been implicated in AD, the potential involvement of exosomes derived from peripheral non-neural tissues/organs in the onset and progression of AD is an area that warrants further investigation. We investigated these links through a series of experiments using TG2576 late plaque murine models of AD that overexpress human amyloid precursor protein (hAPP), with aged and sex matched wild type (WT) c57 BL6 mice as controls. Exosomes were isolated directly from peripheral tissues of these mice, including skin, gut, fat and muscle, among others. Exosomes isolated from primary cell cultures derived from these tissues were also studied for comparison purposes. The size and concentration of these exosomes were evaluated through the use of Nanosight. The cargo of these exosomes was characterized with qPCR and Western Blot to detect RNA and proteins related to AD, such as amyloid beta, phosphorylated-tau, and amyloid precursor protein, among others. The results from the qPCR analysis showed the presence of RNA of hAPP in exosomes isolated from peripheral tissues of TG2576 mice, with similar levels of RNA of mouse amyloid precursor protein (mAPP) observed in treatment and control exosomes. The neurotoxic effects of these exosomes was tested by exposing primary murine embryonic hippocampal neurons to various concentrations of treatment and control exosomes. Cultures exposed to AD exosomes exhibited more pronounced signs of early neurotoxicity. Follow-up studies with qPCR and ELISA indicate that exosomes derived from peripheral AD tissues can modulate the expression levels of mAPP *in vitro* compared to exosomes derived from peripheral tissues of healthy mice. Altogether, these findings suggest a potential role for peripheral tissues in the modulation of AD onset and/or progression presumably via exosome-driven endocrine signaling. Ongoing studies are aimed at further probing the role of AD-associated peripheral exosomes using murine models of this condition as well as human tissue specimens.

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Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.01/E2

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

Title: Impact of tau pathology on cognition in transgenic htau and in C57BL/6J mice after bilateral hippocampal injection of AD-PHF seeds

Authors: *M. LOOS[1], R. CRESPO[2], J. VAN AMEIJDE[2], R. VAN KESTEREN[3], B. ZIERE[2], M. VERHAGE[4], A. B. SMIT[3], W. SCHEPER[4], A. APETRI[2], J. GOUSMIT[5];
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Abstract: Evidence from postmortem and recent PET studies shows that tau pathology in Alzheimer's disease (AD) starts in the entorhinal cortex and spreads throughout the brain. The increase in tau pathology correlates well with the decline in cognitive function. Currently widely used transgenic tauopathy mouse models overexpress human tau with frontotemporal dementia-linked mutations throughout the nervous system. This results in a global induction of tau pathology and behavioral phenotypes unrelated to AD, such as profound motor function impairments. To test antibody-based treatments that can protect against the spreading of tau pathology and concomitant cognitive decline in humans, a mouse model induced by 'seeding' of tau pathology is required that more closely mimics human tau pathology and cognitive decline. The source of the tau seeds as well as the genetic background in which the seeds are injected are expected to have a large effect on the rate at which tau pathology emerges and thereby the tau load. Here we compared the emergence of pathology in wild-type C57BL/6J mice and in htau mice that express all isoforms of human tau and no murine tau (Andorfer et al. 2003) after seeding with tau seeds isolated from human AD brain (AD-PHF) as well as in vitro amplified AD-PHF seeds in 2N4R recombinant tau. Tau seeds were infused bilaterally into the hippocampus to induce pathology and potential cognitive decline. In htau mice, AT8-positive tau structures were observed in hippocampus as well as other brain regions at 3 and 6 months specifically after seeding with AD-PHF, but not after injection of PBS or control brain isolate. In comparison with htau mice, the number of AT8-positive structures was significantly lower in wild-type C57BL6J mice that were seeded with AD-PHF. No thioflavin-s-positive structures were detected at 3 and 6 months after seeding in either model. When compared with transgenic tauopathy mouse models the amount of AT8-positive tau induced by AD-PHF seeding in htau mice was low. No cognitive deficits were observed at 6 months after seeding in either htau or

wild-type C57BL/6J mice in an extensive cognitive test battery. In conclusion, seeding of AD-PHF by bilateral injection induced tau pathology in htau transgenic mice to a greater extent than in C57BL6J mice, but no cognitive impairment in either htau or C57BL/6J mice 6 months after seeding.

Disclosures: **M. Loos:** A. Employment/Salary (full or part-time):; Sylics (Synaptologics BV). **R. Crespo:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson and Johnson. **J. van Ameijde:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson and Johnson. **R. van Kesteren:** None. **B. Ziere:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson and Johnson. **M. Verhage:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sylics (Synaptologics BV). **A.B. Smit:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Sylics (Synaptologics BV). **W. Scheper:** None. **A. Apetri:** A. Employment/Salary (full or part-time):; Janssen Pharmaceutical Companies of Johnson and Johnson. **J. Gousmit:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.02/E3

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

Support: Régions Hauts-de-France
Université Lille
Inserm
CNRS
Labex DISTALZ
LICEND

Title: The role of a new truncated tau species in pathological process of Alzheimer’s disease

Authors: *L. BUEE, **S. GUEDJDAL**, M. DERISBOURG, S. EDDARKAOUI, F. VERMON, R. CAILLIEREZ, S. BEGARD, V. GOMEZ-MURCIA, E. FAIVRE, D. BLUM, M. HAMDANE;
Univ. Lille, Inserm, CHU Lille, UMR-S 1172 – Alzheimer & Tauopathies, Lille, France

Abstract: Neurofibrillary degeneration (NFD), which is one of the Alzheimer’s disease (AD) hallmarks, is mainly composed of aggregated Tau proteins. Mechanisms leading to Tau aggregation are not clearly elucidated. Some studies indicated that Tau truncation could have an etiological role in the pathological process of AD. Recently, we have identified new N-

terminally truncated Tau species. Our preliminary data have shown this new Tau species to be a signature feature of AD. In order to establish whether this Tau species has an instrumental role in Tau pathology development, we have performed stereotaxic injections of lentiviral vectors (LV) expressing full-length Tau and truncated Tau species into the hippocampus of wild-type and Tau-transgenic mice. Our immunohistochemistry analyses of brain sections, performed 2 months post injections have showed that Tau proteins are stably expressed in neurons within the whole hippocampus and that the N-terminally truncated Tau species is detected in regions that are relevant to synaptic plasticity and memory. Moreover, this new Tau species is able to potentiate Tau aggregation. Otherwise, we have showed in Thy-Tau transgenic mice that neutralization of this new Tau specie, using a passive immunotherapy approach, has a beneficial effect towards memory and Tau pathology. Overall, our data indicated that this truncated Tau species is involved in Tau pathology development and is a valuable therapeutic target.

Disclosures: **L. Buee:** None. **S. Guedjdal:** None. **M. Derisbourg:** None. **S. Eddarkaoui:** None. **F. Vermon:** None. **R. Caillierez:** None. **S. Begard:** None. **V. Gomez-Murcia:** None. **E. Faivre:** None. **D. Blum:** None. **M. Hamdane:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.03/E4

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

Title: Enhanced secretion of cleaved tau from cultured neuronal cells by amyloid-β overproduction

Authors: *T. IKEUCHI[1], **T. ISHIGURO**[1], K. KASUGA[1], Y. HIGUCHI[1], N. MEZAKI[2], T. MIURA[1], T. TOKUTAKE[1], O. ONODERA[1];
[1]Niigata University, Brain Res. Inst., Niigata, Japan; [2]Niigata University, Brain Res. Institiute, Niigata, Japan

Abstract: [Objectives] Aberrant proteins pathologically accumulated in brains of Alzheimer's disease (AD) are amyloid-β (Aβ) and phosphorylated tau. Recent studies have suggested that secretion of tau is an important process in the propagation of tau pathology in AD brains. However, the regulation of tau secretion in neurons has not been elucidated. In this study, we attempted to clarify the mechanism of tau secretion from neuronal cells and the effect of Aβ overproduction to the tau secretion. [Methods] Neuro 2a (N2a) cells which stably express human tau (4R1N) were established. Plasmid DNA encoding human *APP* wild type (*APP*-wt) or *APP* Swedish mutation (*APP*-swe) was transiently transfected into N2a cells. After the transfection, the lysate and culture medium were collected. Secreted and intracellular tau was examined by immunoblot analysis using anti-tau antibodies. γ-Secretase inhibitor (DAPT) was used to inhibit

Aβ production. [Results] Intracellular full-length tau was detected by both N-terminal and C-terminal antibodies against tau in the lysate of N2a cells stably expressing human tau. Secreted tau was detected by N-terminal antibody, but not by C-terminal antibody. Secretion of cleave tau was enhanced by transfection of APP-wt or APP-swe. Treatment with γ-secretase inhibitor (DAPT) attenuated secretion of cleaved tau which was induced by APP-wt transfection. [Conclusion] Cleaved tau is secreted from cultured neuronal cells in physiological condition. Secretion of fragmented tau from cultured neuronal cells was enhanced by Aβ overproduction, which may be relevant to the propagation of tau pathology in AD brain.

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Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.04/E5

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

Support: NIH grant NS090993

Title: The tau_{45-230} fragment induces morphological and functional changes in astrocytes associated with their activation in the context of Alzheimer's disease

Authors: *A. B. FERREIRA, C. PARKER;
Cell and Mol. Biol., Northwestern Univ., Chicago, IL

Abstract: We have shown that tau_{45-230} induces neurodegeneration followed by cell death in the context of Alzheimer's disease (AD) and related disorders. Our previous studies indicated that tau_{45-230} is associated with the cytoskeleton and membrane-bound organelles in hippocampal neurons. This subcellular localization underlies the neurotoxicity of this tau fragment by modifying not only the composition and stability of microtubules and actin filaments, but also the axonal transport of organelles. On the other hand, no data are available regarding the presence and/or the effects of this tau fragment in astrocytes in the AD brain. To get insights into a potential role of tau_{45-230} in glia cells, we first immunostained sections obtained from temporal cortex of AD subjects and age-matched controls using the specific tau_{45-230} antibody recently generated in our laboratory. As expected, no tau_{45-230} immunoreactivity was detected in either neurons or astrocytes in control sections. On the other hand, strong immunoreactivity for this tau fragment was detected in degenerating neurons in AD sections. Tau_{45-230} immunoreactivity was also localized in astrocytes in these AD brain sections. To investigate the effects of tau_{45-230} in astrocytes, glial cultures obtained from embryonic day 18 (E18) pregnant rats were transfected with tau_{45-230}-GFP. Changes in the morphology and gene expression in transfected glial cells

were assessed by means of quantitative Western blot, RT-PCR, and immunocytochemistry analyses. Untransfected cultured astrocytes were used as controls. Our results showed that the expression of tau_{45-230} in astrocytes induced the formation of multiple short astrocytic processes. These morphological changes were associated with the significant up-regulation of GFAP and vimentin, markers of astrocyte activation. Furthermore, the presence of this neurotoxic tau fragment was associated with the expression of pro-inflammatory factors in these glia cells. Together, these results suggest that tau_{45-230} could activate astrocytes contributing to the propagation of the disease process in AD. *This work was supported by NIH grant NS090993 to AF.*

Disclosures: **A.B. Ferreira:** None. **C. Parker:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.05/E6

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

Support: Research Foundation-Flanders (FWO grant G.0D76.14)
2016-NIRG-396583

Title: Characterization of synaptic function and behavior of a novel wild-type human tau knock-in mouse model, crossbred with 5xFAD mice

Authors: *D. K. BALSCHUN[1], S. BARENDRECHT[2], A. SCHREURS[1], V. SABANOV[1], S. GEISSLER[2], H.-U. DEMUTH[2], S. SCHILLING[2], H. CYNIS[2];
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Abstract: Although preclinical research has resulted in many new therapeutic approaches, their translation mostly failed. One of the reasons is the lack of animal models that sufficiently reproduce the complexity of human AD and the response of human brain circuits to novel treatment approaches. We generated a novel human wild-type tau knock-in model by whole gene replacement and crossed it with the 5xFAD strain to strongly drive Aß-triggered pathology. Mice of both genders at the age of 6 to 8 months were analyzed by histopathological, biochemical, behavioral and electrophysiological methods.
The pathology of 5xFADxhtau-KI at 6-8 months resembled the one found in 5xFAD mice despite human tau expression in cortical and hippocampal neurons. Thus, the model is suitable to study the interaction of human tau and human APP/PS1 in a high-amyloid background. With regard to tau pathology, only a few markers of tau phosphorylation are present in 5xFADxhtau-KI mice. PHF-tau seems to be absent in these mice. At the behavioral level, htau-KI mice

showed normal WT-like cognitive performance. 5xFADxhtau-KI mice, in contrast, displayed cognitive deficits in the Morris water maze. The electrophysiological studies provided clear indications of impaired synaptic plasticity, as significant LTP deficits were found in htau-KI, 5xFADxhtau-KI and 5xFAD mice but basal synaptic transmission was unchanged. In addition to the predominantly postsynaptic deficit in LTP, we found upregulated mIPSC frequencies in all three experimental mouse models and an increased mEPSC frequency in htau-KI mice. These changes are indicative of presynaptic activation of GABAergic and glutamatergic transmission, respectively, in all three mouse lines. Further experiments are required to reconcile these unexpected findings at the mechanistic level. Given the similar degree of synaptic impairment of htau-KI and 5xFADxhtau-KI, our data suggest that amyloid pathology does not aggravate human Tau-induced synaptic dysfunction at this age.

Disclosures: **D.K. Balschun:** None. **S. Barendrecht:** None. **A. Schreurs:** None. **V. Sabanov:** None. **S. Geissler:** None. **H. Demuth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Probiodrug AG, Halle. **S. Schilling:** None. **H. Cynis:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.06/E7

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

Support: R01AG049456
1P50 AG047266
SantaFe HealthCare Alzheimer’s Disease Research Center

Title: Exacerbation of tauopathy in a mouse model of Alzheimer's disease

Authors: ***B. ULM**[1,2,3], G. XU[1,2,3], S. FROMHOLT[1,2], J. HOWARD[1,2], D. BORCHELT[1,2,3], J. LEWIS[1,2,3];
[1]Dept. of Neurosci., Univ. of Florida, Gainesville, FL; [2]Ctr. for Translational Res. in Neurodegenerative Dis., Gainesville, FL; [3]McKnight Brain Inst., Gainesville, FL

Abstract: *Rationale and Objective:* Alzheimer’s disease (AD) is diagnosed based on the presence of amyloid plaques and neurofibrillary tangles composed of tau. While tau aggregates are primary pathologies in many other neurodegenerative diseases, the presence of extracellular amyloid beta (Aβ) deposits sets AD apart. Studies of familial AD patients has largely demonstrated that amyloid pathology precedes tau pathology, but replicating this temporal relationship of familial AD in mouse models has been challenging.
Methods: In the present study, we generated a mouse model with both hallmark pathologies of

AD, by crossing the APPswe-PS1dE9 model of Aβ amyloidosis with mice that express 0N4R P301L human tau under transcriptional regulation of a doxycycline-suppressible system (rTg4510 mice). From conception onward, doxycycline was administered to suppress transgenic tau expression, while allowing Aβ pathology to progress (14-15 months). Thereafter, doxycycline administration was halted, allowing for induction of human P301L tau expression for the following 6 months of age.
Results: The APPswe-PS1dE9/rTg4510 mice (14-15 months transgenic tau suppression, 6 months transgenic tau expression, n=8) exhibited an exacerbated tau pathology compared to rTg4510 mice expressing only mutant tau with the same treatment (n=9). The exacerbation of tau pathology in this model recapitulates the chronological progression of pathology proposed in the amyloid cascade hypothesis and demonstrates the priming effects of early amyloid pathology on late-life tau pathology. Studies to assess both inflammatory and neurodegenerative changes are ongoing.

Disclosures: B. Ulm: None. **G. Xu:** None. **S. Fromholt:** None. **J. Howard:** None. **D. Borchelt:** None. **J. Lewis:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.07/E8

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

Support: NIH Grant 1R01NS087142-01
Emory ADRC

Title: Tau induces neurodegeneration in Alzheimer’s disease through the sequestration and inhibition of LSD1 function

Authors: *D. J. KATZ, A. K. ENGSTROM, A. C. WALKER, R. A. MOUDGAL, D. A. MYRICK, S. M. KYLE;
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Abstract: Alzheimer’s disease (AD) is an irreversible, progressive brain disorder caused by neuronal cell death in the cortex and hippocampus. AD is characterized by the aberrant accumulation of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau (NFTs). However, the molecular mechanism by which NFTs lead to neuronal cell death remains unclear. Surprisingly, we found that the histone demethylase LSD1 is mislocalized to NFTs in AD cases and is completely depleted from the nucleus in the degenerating cortical neurons of PS19 Tauopathy mice. This suggests that NFTs may interfere with LSD1 function by sequestering LSD1 in the cytoplasm. To determine if this interaction is functional, we deleted

LSD1 in adult mice. Loss of LSD1 systemically in adult mice is sufficient to recapitulate many aspects of AD, including widespread neuronal cell death in the hippocampus and cortex, learning and memory defects, and global gene expression changes that match AD cases. If Tau is functioning through the sequestration of LSD1, then reducing LSD1 in PS19 Tauopathy mice should make these mice more sensitive to aggregating Tau. Consistent with this, we find that reducing LSD1 in PS19 mice decreases survival, exacerbates paralysis, and increases neurodegeneration. Reducing LSD1 also exacerbates the genome-wide expression changes induced by the PS19 Tau transgene. Based on these data, we propose the following model: pathological Tau leads to neuronal cell death in AD by sequestering LSD1 in the cytoplasm and interfering with the continuous requirement for LSD1 to epigenetically repress transcription associated with alternative cell fates. If this model is correct, then overexpressing LSD1 should make it more difficult for pathological Tau to deplete LSD1 from the nucleus. This would be expected to delay the ability of Tau to kill neurons. Strikingly, we find that viral overexpression of LSD1 in hippocampal neurons of PS19 mice at 8.5 months, when Tau aggregates have already formed, is sufficient to suppress Tau induced neurodegeneration and block the Tau induced immune response through 11 months. This work establishes LSD1 as a major downstream effector of Tau mediated neurodegeneration and a highly promising target for therapeutic intervention in AD.

Disclosures: D.J. Katz: None. **A.K. Engstrom:** None. **A.C. Walker:** None. **R.A. Moudgal:** None. **D.A. Myrick:** None. **S.M. Kyle:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.08/E9

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

Support: CNPq
FAPERJ
INTT

Title: Connections between the endoplasmic reticulum stress and tau phosphorylation in Alzheimer’s disease models

Authors: *V. BODART-SANTOS[1,2], M. S. GOMES[1], A. F. BATISTA[1], B. B. NOVO[1], F. G. DE FELICE[1,3];
[1]Inst. of Med. Biochem., [2]Inst. of Biomed. Sci., Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [3]Dept. of Psychiatry, Queen's Univ., Kingston, ON, Canada

Abstract: Alzheimer's disease (AD) is caused by several different factors and the pathological endpoint is usually characterized by protein aggregated, like amyloid beta peptide as senile plaques and the intraneuronal accumulation of hyperphosphorylated tau protein as neurofibrillary tangles. A predominant hypothesis in the AD field is that tau hyperphosphorylation, misfolding, and aggregation into tangles impair synaptic plasticity and contribute to neurodegeneration. Our group showed that amyloid beta oligomers (AbOs) increase tau phosphorylation levels in primary hippocampal cultures and in frontal cortex of a non-human primate model of AD, and induce cognitive deficits through a neuronal endoplasmic reticulum stress (ER stress)-related pathway. Other studies showed that ER stress pathways is activate in pretangle hippocampi from AD patients, but the connection between ER stress and tau hyperphosphorylation it is still unclear. In this work, we used primary hippocampal cells to show that the induction of tau phosphorylation by okadaic acid, a PP2A inhibitor, increase the phosphorylation of ER stress related protein PERK, and using the pharmacological ER stress inducer, thapsigargin, the tau phosphorylation levels are increased. We observe that treatment with 4-phenyl butyric acid (4-PBA), an ER stress attenuator, reduce both tau and eukaryotic initiation factor 2 alpha (eIF2a) phosphorylation induced by AbOs *in vitro*, highlighting an important link between the ER stress and tau pathology in AD. To investigate this connection *in vivo*, we used a well-established model in our lab, consisting of a single injection of an AbOs suspension intracerebroventricularly (i.c.v.). Mice injected with AbOs present cognitive impairment observed in different memory tasks that starts soon after the first 24 hours post-injection. Our results indicate that AbOs can trigger the tau phosphorylation in mice hippocampus 7 days after injection and the treatment with 4-PBA (intraperitoneally) prevents AbOs-induced memory loss in the Novel Object Recognition (NOR) task. We found that in a manner similar to AbOs, i.c.v. injection of thapsigargin, promote a memory loss in the NOR task that is accompanied by eIF2a and tau phosphorylation in mice hippocampus, but 4-PBA treatment was able to prevent both *in vivo*. Together our data indicate that tau phosphorylation and ER stress can be activate in parallel by different mechanisms, and the ER stress attenuation presents an alternative to prevents tau hyperphosphorylation in the brain with direct benefits on memory.

Disclosures: V. Bodart-Santos: None. **M.S. Gomes:** None. **A.F. Batista:** None. **F.G. De Felice:** None. **B.B. Novo:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.09/E10

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

Title: Development of a Tau seeding model in the P301S-PS19 transgenic mouse

Authors: *G. DAS DORES, A. HUGOT, M.-H. GANDON, K. LLOPIS, L. ABJEAN, F. IOP, A. FRANÇOIS, R. BILLIRAS, P. MACHADO, N. RIBEIRO PALHA, F. PANAYI, R. JEGGO; Neuropsychiatry Ctr. for Therapeut. Innovation, Inst. De Recherches Servier, Croissy-sur-Seine, France

Abstract: Background: Neuropathogical hallmarks of Alzheimer's disease include intracellular neurofibrillary, tau-containing tangles, extracellular β-amyloid-containing plaques and a likely interrelated impairment of synaptic structure and function. Since many clinical trials aimed at clearing neurotoxic species of β-amyloid have failed to demonstrate efficacy, tau-based treatments have become a point of increasing focus, including the development of tau-aggregation inhibitors. In order to characterize such agents and *in vivo* validate novel tauopathy-targeting hypotheses, well-established rodent models are essential. Accordingly, we developed *in vivo* disease-relevant models of tau aggregation by using tau seeds derived from transgenic mouse tissue. **Methods**: Pathological tau was extracted from 9 months old Tau-P301S mice (PS19 line) and used as seeds to promote aggregation in young Tau-P301S mice. Different experimental conditions have been evaluated (number of injections, different brain areas and time points) to promote tau pathology formation. Tau aggregates were biochemically measured by a homogenous time-resolved fluorescence (HTRF) assay (Cisbio) and using our in-house ultra-sensitive assays with the SIngle MOlecular Array (SIMOA™) technology to quantify total tau aggregation and the pathological tau conformation, MC1. Histologically, specific tau staining was performed by immunochemistry (AT8 and MC1 markers) to evaluate tau pathology. **Results**: Tau seeds derived from P301S-PS19 mice were able to induce progressive tau aggregate formation 3 months post-injection. A significant increase of tau aggregates was observed with the HTRF and SIMOA assays. Moreover, intense MC1 and AT8 staining was also detected 3 months post-injection. **Conclusions**: We have developed an inducible *in vivo* model of tau aggregation using tau seeds derived from TauP301S-PS19 transgenic mice. Complementary studies are currently underway to optimize our experimental conditions in order to reduce potential variability due to different seed preparations or intracerebral injections. Finally, the development of such an induced-tauopathy mouse model may be very useful to assess in vivo efficacy of small molecules inhibitors of tau aggregate formation.

Disclosures: G. Das Dores: None. **A. Hugot:** None. **M. Gandon:** None. **K. Llopis:** None. **L. Abjean:** None. **F. Iop:** None. **A. François:** None. **R. Billiras:** None. **P. Machado:** None. **N. Ribeiro Palha:** None. **F. Panayi:** None. **R. Jeggo:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.10/E11

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

Support: NIH Grant RF1AG05300 to S.M.S
NIH Grant R01AH034924 to S.M.S
Falk Trust to S.M.S
Böhringer Ingelheim Fonds PhD fellowship to S.H.N

Title: Effect of Pyk2 gene on the spreading of human Alzheimer tau seeds in mouse brain

Authors: *S. NIES[1,2], C. HERBER[1], S. M. STRITTMATTER[1];
[1]CNNR Program, Yale Univ., New Haven, CT; [2]Eberhard Karls Univ. of Tübingen, Tübingen, Germany

Abstract: Alzheimer's disease (AD) is a debilitating neurodegenerative disease that can be distinguished from other dementias through its pathological hallmarks: amyloid-β (Aβ) plaques and neurofibrillary tangles consisting of hyperphosphorylated protein tau. Both proteins are believed to contribute to the molecular causes of AD, with current hypotheses favoring Aβ acting upstream of tau. Nevertheless, the underlying molecular mechanisms – and whether and how the two pathologies are connected – are still under investigation.
Most AD transgenic mouse models have the caveat of overexpressing mutated tau or Aβ. This leads to elevated levels of these proteins from birth, which does not faithfully recapitulate the etiology of human AD. Recently, Virginia Lee's lab has developed a protocol to inject hyperphosphorylated tau extracted from *post mortem* brain tissue of AD patients into mice. This hyperphosphorylated human tau serves as a seed, corrupting endogenous mouse tau into tangles and leading to its spreading even in non-transgenic mice and might thus be able to provide a better model for tau.
We utilized this technique to compare the spreading pattern and density of neurofibrillary tau tangles in mice with various genetic mutations pertaining to proteins implicated in AD. We injected 3-month-old C57BL/6J (WT), Pyk2 null (PTK2B null; Pyk2 KO) and APPswe/PS1ΔE9 (APP/PS1) mice with tau lysates from aged-matched control or AD patient brains (n =10 mice per genotype and lysate, equal male-female ratio) into the hippocampus and cortex (bregma: -2.5 mm, lateral: + 2.0 mm, depth: -2.4 and -1.4 mm). Afterwards, animals were kept for 6 months, perfused with PBS and brains were fixed in 4% PFA. Brains were cut into 40 μm thick sections, then DAB stained with a phospho-tau antibody and immunohistochemically stained for microglial or astroglial activation. We were able to replicate the tau spreading seen in the published data from the Lee lab, though quantitatively at a lower density. We do not see increases in astrogliosis or microglial activation when comparing non-injected, control injected and human AD tau injected mice. When comparing different strains, we observed no difference in tau spreading pattern or overall number of affected neurons in APP/PS1, Pyk2 KO or WT mice injected with human tau. In these studies, neither Aβ plaques nor absence of Pyk2, a part of an Aβ-induced downstream signaling cascade, had a direct impact on tau spreading.

Disclosures: S. Nies: None. **C. Herber:** None. **S.M. Strittmatter:** Other; holds intellectual property rights related to Prion protein, mGluR5, Fyn and Pyk2 in Alzheimer Disease treatment and is a founder of Allyx Therapeutics with equity ownership.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.11/E12

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

Title: Characterization of Alzheimer brain-derived pathological forms of tau and application to anti-tau antibody discovery

Authors: *H. PATEL, N. VENKAT, J. WU, T. KWON, J. MANOS, K. TITTERTON, C. PREISS, H.-Y. WU, X. LANGLOIS, K. YANAMANDRA;
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Abstract: Alzheimer's disease (AD) and other tauopathies are characterized by abnormal phosphorylation and aggregation of tau protein, which is correlated with neurodegeneration and cognitive decline in AD. There is convincing evidence that pathological seed-competent tau can propagate along trans-synaptically connected regions leading to disease progression. These transmitted tau aggregates function as seeding templates to direct misfolding of normal endogenous tau in the healthy recipient cells, leading to the propagation of the pathologic tau forms. However, the specific tau conformations or pathological post-translational modifications that drive the seeding and spreading of pathology are currently not well understood. Therefore, the objective of this study was to identify and characterize the pathological tau forms isolated from human AD brain using different extraction methods and to evaluate the behavior of these tau species in various biochemical and cell based assays. For this purpose, we developed assays using ultra-sensitive digital ELISA platform, Single Molecule Array (SIMOA), targeting N-terminal, mid-domain and C-terminal regions of tau to characterize tau profile in human AD brain material. We also compared our assays to the commercially available Homogeneous Time Resolved Fluorescence (HTRF) assay. Hyperphosphorylated tau was quantified using an ELISA platform against AT8-positive tau forms. Seeding competency was evaluated using FRET-based Biosensor HEK293 cells and hTau primary neurons. Using these different platforms, we characterized the pathological behavior of those tau species isolated from human AD brain. Further, these competent tau seeds were used to generate and develop anti-tau antibodies for therapeutic application and biomarker development.

Disclosures: **H. Patel:** A. Employment/Salary (full or part-time):; Abbvie. **N. Venkat:** A. Employment/Salary (full or part-time):; Abbvie. **J. Wu:** A. Employment/Salary (full or part-time):; Abbvie. **T. Kwon:** A. Employment/Salary (full or part-time):; Abbvie. **J. Manos:** A. Employment/Salary (full or part-time):; Abbvie. **K. Titterton:** A. Employment/Salary (full or part-time):; Abbvie. **C. Preiss:** A. Employment/Salary (full or part-time):; Abbvie. **H. Wu:** A.

Employment/Salary (full or part-time):; Abbvie. **X. Langlois:** A. Employment/Salary (full or part-time):; Abbvie. **K. Yanamandra:** A. Employment/Salary (full or part-time):; Abbvie.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.12/E13

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

Title: The effect of progranulin reduction on tau pathology and tau-associated deficits in a mouse model of tauopathy

Authors: *H. TAKAHASHI[1], Z. A. KLEIN[1], S. M. BHAGAT[1], T. IKEZU[2], S. M. STRITTMATTER[1];
[1]CNNR Program, Yale Univ., New Haven, CT; [2]Pharmacol. and Neurol., Boston Univ. Sch. of Med., Boston, MA

Abstract: Progranulin (PGRN) is a secreted glycoprotein expressed by neurons and microglia in the central nervous system and is implicated in Alzheimer's disease (AD) as well as frontotemporal dementia and neuronal ceroid lipofuscinosis. Genetic studies demonstrate an association of the common progranulin gene (*GRN*) rs5848 variant with increased AD risk. We have previously found that the *GRN* AD risk variant has no significant effects on florbetapir positron emission tomographic amyloid imaging as well as cerebrospinal fluid (CSF) amyloid-β (Aβ) 1-42 levels, whereas it is associated with increased CSF total tau levels in the ADNI human subjects. In line with the human evidence, subsequent analyses using the APPswe/PS1ΔE9 mice also showed no exacerbating effects of PGRN deficiency on Aβ pathology, whereas we observed an increase in tau AT8 and AT180 pathologies in PGRN-deficient mice with adeno-associated-virus-mediated human P301L tau expression, independent of Aβ (Takahashi et al. 2017). These human and rodent data suggest that PGRN reduction may increase AD risk by exacerbating tau pathology, rather than by accelerating Aβ accumulation.
In this study, to further investigate effects of PGRN reduction on tau pathology and tau-mediated phenotypes including behavior deficits, gliosis, and neurodegeneration, we used a P301S tauopathy (PS19) mouse model that overexpresses 1N4R human P301S tau and generated PS19 mice with PGRN haploinsufficiency (PS19 *Grn*+/-) or complete loss (PS19 *Grn*-/-). At 7.5 months of age, we observed a significant body weight loss in PS19 *Grn*-/- mice, compared to mice with the other genotypes. In addition, mortality due to tau transgene-mediated hindlimb paralysis was also increased in PS19 *Grn*-/- mice, compared to PS19 *Grn*+/+ mice at 10 months of age. As both *Grn*-/- and PS19 mice are reported to exhibit a disinhibiton phenotype, we tested these animals in an elevated plus maze. We found that PS19 *Grn*-/- mice entered more frequently and spent more time in the open arms, compared to *Grn*-/- or PS19 *Grn*+/+ mice at 10 months of

age, suggesting an exacerbation of the disinhibition phenotype in PS19 *Grn*-/- mice. These animals were then sacrificed and the brains were dissected out and one hemisphere was snap-frozen for biochemical and RNA analyses and the other was fixed with 4% paraformaldehyde for immunohistochemistry. Future experiments will address whether tau pathology and tau-mediated gliosis and neurodegeneration are altered in PS19 *Grn*+/- or PS19 *Grn*-/- mice.

Disclosures: H. Takahashi: None. **Z.A. Klein:** None. **S.M. Bhagat:** None. **T. Ikezu:** None. **S.M. Strittmatter:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.13/E14

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

Support: NIH Pioneer DP1AG047744-01
AARF-17-533294

Title: The calcium-containing smooth endoplasmic reticulum is a focus of risk factors for early and late onset Alzheimer's disease

Authors: *D. DATTA[1], Y. M. MOROZOV[4], J. I. ARELLANO[2], M. WANG[6], C. VAN DYCK[3], A. F. ARNSTEN[5];
[2]Neurobio., [3]Psychiatry, [1]Yale Univ., New Haven, CT; [4]Dept Neurobiol, [5]Yale Univ. Sch. Med., New Haven, CT; [6]Yale Univ. Sch. of Med., New Haven, CT

Abstract: TREM2 is a risk factor for late onset Alzheimer's Disease (AD). Current research from mouse models has focused on the role of microglial TREM2 in reducing extracellular Aβ. However, mouse models do not provide the opportunity to explore the newly evolved association cortices that are the most vulnerable to AD neurodegeneration and tau pathology. Our recent data have shown that aging rhesus monkeys exhibit the same qualitative pattern and sequence of tau pathology as humans, with neurofibrillary tangles and autophagic degeneration. Thus, aging monkeys can be uniquely helpful in using high quality immunoelectron microscopy to elucidate the molecular events in association cortex that increase risk for AD pathology. Our new data from aging monkey dorsolateral prefrontal cortex (dlPFC) indicate that TREM2 is found not only in glia, but in neurons, focused on the calcium-storing smooth endoplasmic reticulum (SER). The SER is also the focus of presenilin (PS1, PS2) expression, the genes most commonly linked to early onset, autosomal dominant AD. This nexus of genetic risks suggests that calcium dysregulation is a key factor in AD neurodegeneration, a mechanism that has been recognized but underemphasized in the AD field. Our new data also show that the SER is also a focus of age-related pathology in association cortex, with loss of PDE4D from the SER in spines and

dendrites, and increased PKA phosphorylation of type II ryanodine receptors (RyR2) on the SER at S2808, which causes calcium "leak". We also find evidence of increased PKA phosphorylation of tau at S214, an important step that causes tau to detach from microtubules and aggregate, and primes tau for hyperphosphorylation and neurofibrillary tangle formation. As with pS2808RyR2, pS214Tau aggregates on the SER early in the aging process. Thus, early onset (PS1), late onset (TREM2) and aging, all target the SER in the association cortical synapses most vulnerable to AD pathology. Finally, restabilizing pS2808RyR2 with S107 treatment to reduce calcium "leak", enhances *in vivo* pyramidal delay cell firing and working memory function in rhesus macaques. Therefore, illuminating the cascade of events in the aging cortex may provide an opportunity for therapeutic intervention at early stages of pathology.

Disclosures: D. Datta: None. **Y.M. Morozov:** None. **J.I. Arellano:** None. **M. Wang:** None. **C. van Dyck:** None. **A.F. Arnsten:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.14/E15

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

Title: Evaluation of the axolotl as a novel model to study physiological response to neurodegenerative diseases

Authors: *L. JAMES[1,2,3], A. WALKER[1,2,3], T. POLVADORE[4], M. MADEN[4], J. LEWIS[1,2,3]; [1]Ctr. for Translational Res. in Neurodegenerative Dis., [2]Dept. of Neurosci., [3]McKnight Brain Inst., [4]Dept. of Biol. and UF Genet. Inst., Univ. of Florida, Gainesville, FL

Abstract: The axolotl, *Ambystoma mexicanum*, has the ability to regenerate entire limbs, tail, and large portions of organs, making it a widely used model for investigating development and regenerative processes. The axolotl brain exhibits both extensive regeneration and continual production of physiologically healthy and functionally diverse neurons, making it a potentially ideal model for investigating physiological response to neurodegeneration. While the full 32 billion base pair genome was primarily sequenced to identify genes responsible for skin and limb regeneration, we identified homologs for genes associated with neurodegenerative diseases such as *GRN* and *MAPT* to illustrate this model's potential. *GRN* codes for progranulin (PGRN), a 593 AA anti-inflammatory, secreted glycoprotein which can be cleaved into 7.5 cysteine-rich, pro-inflammatory granulins, whereas *MAPT* codes for tau, a 441 AA protein involved in microtubule assembly and stabilization. Using the axolotl-omics genome browser and transcriptome assembly, we identified axolotl genes and transcripts homologous to *GRN* and *MAPT*, coined *ax_grn* and *ax_mapt* which code for ax_pgrn and ax_tau, respectively. We then aligned the protein sequences of PGRN and tau with ax_pgrn and ax_tau using the NCBI Protein BLAST

tools and identified corresponding functional domains. The ax_pgrn is 851 AA long and appears to have 10.5 granulin-like motifs that contain the same number of cysteine residues as human granulins. The ax_tau is 528 AA long and has high conservation in the proline-rich, microtubule binding, and C-terminus regions. The ax_tau binding domain is 94% functionally-equivalent to the binding domain of human tau and the proline-rich regions has a similar ratio of prolines. Currently, size is used as the aging marker in axolotl research, however, we show that axolotls develop lipofuscin, a wear-and-tear pigment used as a marker in human aging. We will characterize lipofuscin in young, old, and regenerated tissue to establish a comparative timescale for immunohistochemical staining and protein immunoblotting. Establishing the axolotl as a novel model to study neurodegenerative disease potentially enables researchers to study evolved mechanisms of combatting neural damage.

Disclosures: L. James: None. **A. Walker:** None. **T. Polvadore:** None. **M. Maden:** None. **J. Lewis:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.15/E16

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

Title: Declines in behavior and cognition as tau is expressed at different times in the adult *drosophila melanogaster* brain

Authors: *D. B. GONZALEZ[1], D. D. LENT[2];
[1]Biol., California State University, Fresno, Fresno, CA; [2]Biol., CSU Fresno, Fresno, CA

Abstract: The fruit fly, *Drosophila melanogaster*, has proven to be a useful model organism for many human neurodegenerative diseases. Here, we use the fruit fly to demonstrate the progressive decline in behavior and cognition associated with Alzheimer's disease (AD). This disease is characterized by Aβ plaques and Neurofibrillary Tangles (NFTs). Our focus in this study is on the tau protein which forms the tangles and may lead to neurodegeneration and a decline in learning and memory. To investigate tau mediated neurodegeneration, we inserted human tau into two specific areas of the fruit flies' brain, the Mushroom body (MB) and the Ellipsoid Body (EB). These areas have homologous structures in mammals (hippocampus and basal ganglia) that have demonstrated to be necessary for various cognitive behaviors. In addition to spatially constraining the expression of tau, we expressed tau at 3 different life stages (young, middle, and elderly). Investigating the effects of tau through several stages of life allows for a better comparison and possibly a better model for AD. Using the temperature and regional gene expressing (TARGET) system, we are able to express tau only during the adult stage of life. All experiments involved using virgin females to avoid confounds of male-male and male-female

interactions during group behavioral assays. A minimum of ten flies of each age group (5 day old, 15 day old, 25 day old) from each of the fly lines (MB, EB), as well as control groups that shared the same genetic background, but did not express tau, were used for behavioral testing. We assessed behavioral and cognitive declines through a series of learning, memory, and planning assays, along with fluorescent microscopy to analyze tau expression in the fly brain. A progressive decline in learning and memory was found within the transgenic fly lines. Tau expression in the brain also increased as age increased. This exploratory research can support a better *Drosophila melanogaster* model of AD, which can serve to advance treatment at the early stage of the disease and help alleviate symptoms in the future.

Disclosures: D.B. Gonzalez: None. **D.D. Lent:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.16/E17

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

Support: Brigham Young University, College of Life Sciences, Mentoring Environment Grant
NIH/NIA 1 R21 AG037843
Brigham Young University, School of Family Life, Gerontology Program
Brigham Young University, Dr. Sarah M. McGinty Neuroscience Graduate Student Research Fellowship
Neurodar, LLC
Limitless Worldwide, LLC

Title: Comparison of 11.7T *ex vivo* with 3T *in vivo* MRI signal intensity of the hippocampus of wild-type, Tau, and PSEN1 individual mice: A pilot study

Authors: *A. SOTELO[1], M. DIAMSE[2], N. HUANG[2], K. S. STEED[3], J. HAMILTON[2], J. WISCO[4];
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Abstract: Alzheimer’s disease (AD) causes tremendous damage to the brain over the course of the life of those afflicted. A major focus of AD research pertains to the development of diagnostic tools and methods to examine subtle pathological changes that occur early in the brain. Improving Magnetic Resonance Imaging (MRI) techniques to visualize brain pathology is an important step toward achieving definitive clinical diagnostic imaging. We have been using

3T MRI to assess the pathological effects of PSEN1 and Tau transgenic mice compared with C57BL6 wild-types (WT) in an animal model for AD. Although *in vivo* imaging in a 3T Siemens Trio produced adequate signal to noise for semi-quantitative analysis in our longitudinal study, we wanted to know the extent of signal gain using *ex vivo* imaging in a 11.7T Bruker 500 MHz magnet. Methods: Of the PSEN1, Tau and WT mice bred for this project, we imaged one post-mortem brain hemisphere from amongst subjects in each cohort that were fed a normal diet and were sacrificed at 6 months into the study. We acquired T1 images at 11.7T; and T2, and T2* images at both 3T and 11.7T. In this pilot study we measured and compared the signal intensity differences of the body of the hippocampus from T2 and T2* images. Measurements were acquired from one axial slice at a level where both the anterior and posterior horns of the lateral ventricles were visible using the analysis software Horos (https://horosproject.org/). Results: We show that 11.7T MRI provides superbly clearer signal to noise of all structures of the brain. The average signal between 11.7T and 3T field strengths within a 2 mm ROI of the hippocampus body in the PSEN1 mouse brain T2 image showed an 840 fold increase, and an 85 fold increase in the T2*. In the Tau mouse brain, T2 showed a 746 fold increase in signal; T2* showed a 95 fold increase in signal. In the WT brain, T2 showed a 646 fold increase in signal; T2* showed a 70 fold increase in signal. Conclusion: Although preliminary, results indicate an approximately linear difference in T2 and T2* signal between 11.7T and 3T MR field strengths, and may indicate that post-mortem imaging at high field strength can be added to our protocol to assess pathological changes in the mice brains across transgene cohorts.

Disclosures: A. Sotelo: None. **M. Diamse:** None. **N. Huang:** None. **K.S. Steed:** None. **J. Hamilton:** None. **J. Wisco:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.17/E18

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

Title: Neuronal N27A cell line expressing mutant tau YFP provides a model for Alzheimer’s disease

Authors: *C. R. FREED[1], S. L. HAMMOND[2], W. ZHOU[3];
[1]Clin. Pharmacol., [2]Univ. of Colorado, Aurora, CO; [3]Dept. of Med., Univ. of Colorado Denver, Aurora, CO

Abstract: The incidence of Alzheimer’s disease is rising as the elderly population increases in the United States and around the world. Brain pathology is defined by extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles of tau protein. Recent studies have suggested that aggregated tau, and not Aβ aggregation, correlates most closely with dementia.

After the failure of many clinical trials targeting Aβ, it is now time to explore treatments that prevent tau pathology. Metabolism of tau can produce hyper-phosphorylation and protein aggregation leading to neuronal toxicity. To model tauopathy *in vitro*, we have used rat neuronal N27A cell lines to stably express either the human P301L mutant tau gene (Mut-tau-YFP) or the wild type tau gene (WT-tau-YFP). These cells can be monitored in live culture by their expression of the YFP gene. We have found that the constitutive expression of the mutant tau gene leads to protein aggregation and formation of large inclusions in every cell, thereby mimicking the neurofibrillary tangles which are present in human Alzheimer's disease. Immunostaining and Western blotting have confirmed that tau is hyperphosphorylated in the Mut-tau-YFP cell line. Interestingly, this sane Mut-tau-YFP cell line can directly secret tau protein into the culture medium. When exposed to oxidative stress, Mut-tau-YFP cells are more vulnerable to cell death than WT-tau-YFP cells. When both cell lines are pre-treated with 150 uM of phenylbutyrate, the drug protects both WT-Tau-YFP and Mut-Tau-YFP cells from hydrogen peroxide-induced cell death. In summary, the N27A rat dopaminergic cell line expressing mutant tau with a YFP reporter can recapitulate the pathological features of tauopathy. This cell line should provide a useful *in vitro* model for studying the molecular mechanisms of tau aggregation and for screening drugs that may have value for treating patients with Alzheimer's disease.

Disclosures: C.R. Freed: None. **S.L. Hammond:** None. **W. Zhou:** None.

Poster

472. Tau: Animal and Cellular Models I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 472.18/E19

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

Support: NIH R01AG053229
Glenn Foundation for Medical Research
Cure Alzheimer's Fund
Alzheimer's Disease Research Center of Mayo Clinic
Ellison Medical Foundation

Title: Genetic ablation of the senescence mediator p16 attenuates tau-mediated neurodegeneration

Authors: *C. F. MEYER[1], S. I. GRAVES[2], T. J. BUSSIAN[2], B. L. SWENSON[1], D. J. BAKER[1,2];
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Abstract: Cellular senescence is a process characterized by an irreversible cell cycle arrest and a distinct secretory phenotype, which can be induced in response to many intracellular and extracellular factors. Traditionally, these cells have been characterized by exhibiting increased expression of the cell cycle inhibitors $p21^{Cip1}$, $p19^{ARF}$, and/or $p16^{INK4A}$. We, and others, have demonstrated that cells expressing $p16^{INK4a}$ actively drive tissue deterioration with natural aging and in several age-associated diseases, including atherosclerosis, osteoarthritis, and neurodegenerative disease in mice. We have used a transgenic mouse model (termed INK-ATTAC) in combination with a tauopathy-based mouse model of neurodegeneration to demonstrate that removal of $p16^{INK4A}$-positive cells prevents tau-dependent pathology and cognitive impairment, suggesting that senescent initiate disease. Here, we demonstrate that genetic deletion of $p16^{INK4A}$ in the background of $MAPT^{P301S}$ PS19 mice also attenuates tau-dependent pathology. Loss of $p16^{INK4A}$ decreases gliosis, p-tau burden, neurofibrillary tangle development, and importantly, preserves hippocampal and cortical neurons resulting in near baseline cognitive function. This work further highlights the importance of $p16^{INK4A}$-dependent cellular senescence in the initiation and progression of tauopathy-based disease, and narrows the scope for further study implicating senescence in the development of other neurodegenerative diseases.

Disclosures: C.F. Meyer: None. **S.I. Graves:** None. **T.J. Bussian:** None. **B.L. Swenson:** None. **D.J. Baker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Unity Biotechnology.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.01/E20

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

Support: NIH NIA U54 AG054349 supplement to UCI MODEL-AD Translational Center for Disease Model Resources
NIH R56 AG062169 (EJB)

Title: Lifespan magnetic resonance imaging of novel mouse models of Alzheimer's disease: Phenotyping and comparisons to healthy aging

Authors: *A. JULLIENNE[1], A. OBENAUS[2,4], J. LEE[5], J. I. SZU[3], E. J. BEHRINGER[4], M. AD CONSORTIUM[3,6,7,8,9];
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Abstract: The Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD) consortium has been established to develop the next generation of Alzheimer's disease (AD) models based on human data. As these models are developed, they are rigorously characterized using genomic, histological, electrophysiological and behavioral measures. Magnetic resonance imaging (MRI) provides multiple contrasts to probe the healthy aging brain of C57BL/6J mice and AD mouse models as they exhibit progressive onset of the disease. Several AD mouse models are being assessed, including 5xFAD (a commonly used model of familial AD) and human amyloid beta (Aß) knock-in mice, wherein the human Aß which forms the characteristic fibrillar plaques of AD is expressed under the murine endogenous promoter. All MODEL-AD mice are compared to age-matched littermates (C57BL/6J) mice at 4, 8, 12 and >18mo (N=8-9/sex/age). Mice underwent high-resolution MRI to assess their phenotype: T2-weighted and susceptibility-weighted imaging (11.7T) were used for brain region volumetric analysis and quantitative analysis of Aß plaque load, and diffusion tensor imaging (DTI, 9.4T) was used to analyze white matter tracts. Emerging data found significant volumetric reductions (~6%) in cerebrum volumes between 8mo-old female C57BL/6J and age-matched 5xFAD mice. Hippocampal volumes were significantly reduced in 4mo-old males but not females when comparing C57BL/6J to 5xFAD mice. DTI metrics that report tissue features, such as fractional anisotropy, radial, axial and mean diffusivity will evaluate the progressive alterations in AD mouse models over their lifespan. Preliminary tractography mapping circuits from hippocampal CA1 to the subiculum found sex-specific differences in the number and density of tracts (streamlines) in healthy 4mo C57BL/6J mice. Such novel sex differences will be analyzed in our novel AD mouse models as well as age-matched healthy control mice. In summary, phenotyping using multimodal MRI can identify altered brain connectivity and regional tissue metrics across the mouse lifespan in healthy aging and in AD models. These MRI approaches can lead to clinically translatable tools for assessment of AD progression in human patients. For more information, see model-ad.org.

Disclosures: **A. Jullienne:** None. **A. Obenaus:** None. **J. Lee:** None. **J.I. Szu:** None. **E.J. Behringer:** None. **M. AD consortium:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.02/E21

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

Support: NIA U54 AG054345-01

Title: Development and characterization of novel mouse models of late-onset Alzheimer's disease

Authors: *M. SASNER[1], D. GARCEAU[1], K. KOTREDES[1], A. OBLAK[2], C. INGRAHAM[2], D. SONI[2], H. WILLIAMS[1], A. REAGAN[1], A. UYAR[1], R. PANDEY[1], C. PREUSS[1], B. LOGSDON[4], P. R. TERRITO[3], G. CARTER[1], B. T. LAMB[2], G. R. HOWELL[1];
[1]The Jackson Lab., Bar Harbor, ME; [2]STARK Neurosci. Res. Inst., [3]Radiology and Imaging Sci., Indiana Univ. Sch. of Med., Indianapolis, IN; [4]Sage Bionetworks, Seattle, WA

Abstract: AD therapy development efforts have consistently failed, despite success in preclinical trials in animal models. This may have many causes, but more predictive animal models would certainly be beneficial. The Model Organism Development and Evaluation for Late-onset AD (MODEL-AD) Center was created to develop, characterize, and distribute more precise preclinical models for late-onset AD (LOAD). Our approach is to engineer mouse models to express combinations of genetic variants identified in human LOAD populations in genome-wide association studies (GWAS). These are being generated into a model that predisposes to AD risk by expressing humanized APOE4 and mutant Trem2. In the future, we will also include humanized APP and MAPT (Tau). GWAS variants are prioritized to impact discrete pathways (e.g. neuroinflammation, lipid metabolism, etc.). Models are prioritized for comprehensive phenotyping based on a newly designed nanoString transcriptomics panel compiled from human post mortem co-expression data from the AMP-AD consortium. This approach enables us to correlate transcript profiles in the mouse models to key human disease processes and pathways. We have edited human AD risk variants into the corresponding mouse genes for *Abca7, Clasp2, CR1, Kif21b, Mthfr, Mtmr4, Plcg2, Shc2, Slc6a17, Snx1* and *Sorl1*. Knockouts of *Abca7, Ceacam1, Il1rap*, Meox2 and *Plcg2* have also been created to model human loss of function variants in the mouse. Analysis at 4, 8, and 12 months shows that some of the AD-associated transcriptomic modules are disrupted in an age-dependent manner, including immune and DNA-repair pathways. The most promising models (as well as existing fAD mouse models) are being phenotyped to 24 months of age using clinically relevant measures including transcriptomics, proteomics, metabolomics, biomarkers in CSF and blood, neuropathology, *in vivo* imaging (for amyloid, tau, blood flow and glucose metabolism) and cognitive assays. This will determine key phenotypes and the therapeutic window for each model in a comprehensive manner. We plan to later combine variants that impact various AD-relevant pathways. Through introducing combinations of human AD risk variants into mice, we expect to create new models that provide more precise and relevant translational models for preclinical development. All models are made available for both academic and for-profit use from The Jackson Laboratory, and all validation data will be shared via the AMP-AD knowledge portal. For more information see www.model-ad.org.

Disclosures: **M. Sasner:** None. **D. Garceau:** None. **K. Kotredes:** None. **A. Oblak:** None. **C. Ingraham:** None. **D. Soni:** None. **H. Williams:** None. **A. Reagan:** None. **A. Uyar:** None. **R. Pandey:** None. **C. Preuss:** None. **B. Logsdon:** None. **P.R. Territo:** None. **G. Carter:** None. **B.T. Lamb:** None. **G.R. Howell:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.03/E22

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

Support: U54AG054349

Title: Characterization and deep phenotyping of the 5xfAD mouse model by MODEL-AD

Authors: *S. FORNER[1], M. AD CONSORTIUM[1,2,3,4,5];
[1]Univ. of California Irvine, Irvine, CA; [2]Indiana Univ., Indianapolis, IN; [3]Univ. of Pittsburgh, Pittsburgh, PA; [4]Jackson Lab., Bar Harbor, ME; [5]Sage Bionetworks, Seattle, WA

Abstract: The Model Organism Development and Evaluation for Late-Onset Alzheimer's Disease (MODEL-AD) has been established as a consortium consisting of University of California Irvine, University of Indiana, University of Pittsburgh, Jackson Laboratory and Sage Bionetworks to develop the next generation of Alzheimer's disease (AD) models and institute a standardized and rigorous process for characterization of animal models. One of the goals is to further characterize and deep phenotype well utilized early onset AD models, such as the 5xfAD model. This model is known for recapitulating many AD-related phenotypes and have a relatively early and aggressive presentation. Behavioral assays, Long-term potentiation (LTP) recordings from acute hippocampal slices, RNA-seq, immunofluorescent histology, and biochemical assays were performed in male/female 5xfAD mice and compared to age-matched littermates (C57BL/6J) mice at 4, 8, and 12 months. 5xfAD mice exhibit robust plaque deposition, present throughout the brain by 4 months of age, with plaque numbers and sizes increasing with age, alongside increases in detergent soluble and insoluble Aβ38, Aβ40 and Aβ42 levels in both hippocampus and cortex. Concomitant with plaque deposition are increases in microglia densities, and expression of GFAP by astrocytes. Reductions in $NeuN^+$ neurons are seen from 4 months of age in the cortex. Female mice show increased plaque and Aβ burden, and associated changes in glial cells, compared to male mice, but this may be due to observed increased transgene expression from the Thy1 promoter in female mice. Strong behavioral deficits are seen in the elevated plus maze from 4 months of age, compared to wild-type controls, as well as robust LTP deficits. In summary, 5xfAD mice have a range of cognitive and motor deficits and severe amyloid pathology. All data sets and protocols will be made widely available to the scientific community. For more information, see model-ad.org.

Disclosures: S. Forner: None. **M. AD Consortium:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.04/E23

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

Support: U54 AG054345

Title: Uncoupling of cerebral blood flow and glucose metabolism in APOE4, TREM2, and APOE4.TREM2 mice

Authors: *P. B. LIN[1], S. A. PERSOHN[2], A. A. BEDWELL[2], L. JIANG[2], K. M. ELDRIDGE[2], R. SPEEDY[2], K. KOTREDES[4], R. PANDEY[4], H. WILLIAMS[4], A. L. OBLAK[3], M. SASNER[4], G. R. HOWELL[4], G. W. CARTER[4], B. T. LAMB[1], P. R. TERRITO[2];
[1]Stark Neurosciences Res. Inst., Indianapolis, IN; [2]Radiology and Imaging Sci., [3]STARK Neurosci. Res. Inst., Indiana Univ. Sch. of Med., Indianapolis, IN; [4]The Jackson Lab., Bar Harbor, ME

Abstract: Alzheimer’s disease (AD) is the most common cause of dementia in the United States. Approximately 95% of patients have sporadic Late-Onset AD (LOAD) which lacks an inheritance pattern. Therefore, identifying phenotypic patterns are critical for understanding disease progression. Apolipoprotein E4 (APOE4), the strongest genetic risk factor of LOAD, increases AD risk by 3-12 fold depending on copy number. Recent GWAS analysis elucidated the LOAD-associated loci on the triggering receptor expressed on myeloid cell 2 (TREM2). APOE is a known ligand to the TREM2 receptor, and the R47H variant could increase the AD risk by 2-3 fold. Preclinical studies of these risk alleles and their phenotypes are underway by MODEL-AD. Using PET/MRI and a novel analytical scheme, we established the perfusion-metabolism profiles across 27 brain regions in both sexes by using ^{64}Cu-PTSM and ^{18}F-FDG in the APOE4 (*APOE4*$^{E4/E4}$), TREM2 (*TREM2*$^{R47H/R47H}$), and double (*APOE4*$^{E4/E4}$.*TREM2*$^{R47H/R47H}$) knockin (KI) mice. Longitudinal analysis comparing 8mo to 4mo time point revealed that male APOE4 mice and both sexes of TREM2 had hypo- perfusion and metabolism, while female APOE4 mice showed an uncoupled hyper-perfusion and hypo-metabolism phenotype, and was correlated to human AD pathology. In the double KI mice, perfusion and metabolism showed a mixed phenotype which was region dependent. Cross-sectional analysis of KI compared to B6 mice at 8mo showed an overall reduced glucose metabolism. Intriguingly, male APOE4, TREM2, and double mice showed hypo-perfusion and metabolism, while female double mice showed metabolic uncoupling compared to B6. Analysis of blood biochemistry in non-fasted mice revealed no significant difference between genotypes in blood glucose level with age. However, APOE4 decreased the blood cholesterol level, including total cholesterol, LDL, and HDL. By contrast, TREM2 decreases the level of non-essential fatty acid in male mice. To

confirm these findings, RNAseq, nanostring, and immunohgistology was peformed. Consistent with the phyotypes described, key genes involved in the regulation of cerebral perfusion, glucose transportation, and metabolism were altered. Moreover, we observed the vascular disruption by immunostaining of endothelial markers. These data suggest that the new perfusion-metabolism strategy may be able to identify AD-related patterns. Moreover, they replicate clinical manifestations of subjects with the same variants. Finally, additional studies are needed to elucidate the mechanisms and etiology of this uncoupling phenomenon.

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Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.05/E24

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

Support: NIH Grant AG054345
NIH Grant AG055104

Title: Multi-phenotype comparison of an APOE4.Trem2*R47H mouse model and human late-onset Alzheimer's disease

Authors: *G. W. CARTER[1], R. S. PANDEY[2], K. P. KOTREDES[1], C. PREUSS[1], H. WILLIAMS[1], A. OBLAK[3], S. J. S. RIZZO[5], P. R. TERRITO[4], M. SASNER[1], G. R. HOWELL[6], B. T. LAMB[7];
[1]The Jackson Lab., Bar Harbor, ME; [2]The Jackson Lab., Farmington, CT; [3]STARK Neurosci. Res. Inst., [4]Radiology and Imaging Sci., Indiana Univ. Sch. of Med., Indianapolis, IN; [5]Univ. of Pittsburg Sch. of Med., Pittsburg, PA; [6]Jackson Lab., Bar Harbor, ME; [7]Stark Neurosciences Res. Inst., Indianapolis, IN

Abstract: Current animal models do not fully recapitulate late-onset Alzheimer’s Disease (LOAD), thus are not ideal for therapy development. To address this, the Model Organism Development and Evaluation for Late-onset AD consortium (MODEL-AD) has created a novel LOAD mouse carrying two common risk alleles. Characterization of this model at young and advanced ages will indicate more appropriate disease mechanisms useful in the treatment of LOAD.
Humanized *APOEe4* and the *Trem2*R47H* mutation, two prominent genetic risk factors for LOAD, were inserted into the genome of C57BL/6J mice to create the B6.*APOEe4.Trem2*R47H*

(B6J.*hAT*) model. Cohorts of B6J.*hAT* (with controls) were established at JAX and IU and aged to 2, 6, 12, and 24 months. At JAX, *in vivo* behavior and wellness assays measured activity, frailty, grip strength, coordination, and cognitive ability. At IU, MRI and PET studies using [18F]-FDG and [64Cu]-PTSM were completed. Post-mortem analyses at both sites included blood chemistry, brain immunohistochemistry, transcriptomics, metabolomics, and proteomics. Data from 'omics experiments were systematically compared to analogous data from the Accelerating Medicines Partnership for Alzheimer's Disease (AMP-AD) human disease cohorts. By 12 months, female B6J.*hAT* mice displayed reduced frailty index scores, a measure of aging and vulnerability, suggesting a protective phenotype. B6J.*hAT* and B6.*APOEe4* mice showed decreased levels of total cholesterol, LDL, and HDL at multiple time points - an effect of the *APOEe4* allele that has been reported previously. We also observed a novel splicing event in mice expressing the *Trem2**R47H variant and approximately 50% reduction in TREM2 expression. Global transcriptomics revealed age-related changes in B6J.*hAT* brain samples compared to controls. Differentially expressed genes were enriched in multiple AD-related pathways including immune response, splicesome, and osteoclast differentiation. Proteomic and metabolomics assays further align effects in the mouse models with a subset of changes observed in human post-mortem samples. We observed sex-specific effects from the *APOEe4* allele that generally aligned with LOAD in women.
The MODEL-AD consortium has established a new mouse strain to study the effects of two strong risk factors for LOAD that affect systems-level measures associated with human disease. This model serves a backbone strain for the further addition of LOAD risk alleles to more closely align phenotypes in the mouse to outcomes observed in human AD.

Disclosures: G.W. Carter: None. **R.S. Pandey:** None. **K.P. Kotredes:** None. **C. Preuss:** None. **H. Williams:** None. **A. Oblak:** None. **S.J.S. Rizzo:** None. **P.R. Territo:** None. **M. Sasner:** None. **G.R. Howell:** None. **B.T. Lamb:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.06/E25

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

Support: U54 AG054345

Title: Modeling Trem2 variants in mice

Authors: *A. L. OBLAK[1], H. WILLIAMS[3], K. KOTREDES[3], M. SASNER[3], S. J. SUKOFF RIZZO[4], G. CARTER[3], G. R. HOWELL[5], C. PREUSS[3], A. UYAR[3], R. S. PANDY[3], C. INGRAHAM[1], D. SONI[1], V. JADHAV[1], A. P.-Y. TSAI[1], P. R. TERRITO[2], B. LOGSDON[6], B. T. LAMB[7];

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Abstract: Alzheimer's disease (AD) is the leading cause of dementia. The majority of AD cases are late-onset, but a causal mechanism remains unknown. However, there are likely multifactorial contributors like age, environment and genetics that increase the risk for developing the disease. Genetic factors such as rare variants of TREM2 (triggering receptor expressed on myeloid cells-2) strongly increase the risk of developing AD, confirming the role of microglia in AD pathogenesis. Several studies have examined the mechanisms by which TREM2 and its rare variants affect amyloid and tau pathologies and their consequences in both animal models and in human studies. The Model Organism Development and Evaluation Center for Late-Onset Alzheimer's disease (MODEL-AD) has created a mouse models carrying the Trem2*R47H KI allele using CRISP/Cas9 containing a nucleotide G>A point mutation for amino acid sequence change at R47H into the gene. Mice were aged to 2, 8 and 12 months. In addition, the 5xFAD model was crossed with mice carrying the Trem2*R47H variant. Tissue was analyzed using RNA-sequencing, IP Western Blotting and immunohistochemistry. In mice carrying the R47H variant, there is an alternate splicing event, resulting in a 119bp deletion inside exon 2 and decreased mRNA levels. The deleted segment includes the R47H mutation. This alternate splicing event occurs in some non-mutant mice, but is more prominent in Trem2*R47H samples. This finding suggests an alternate splicing effect on *Trem2* due to R47H mutation. Using IP Western Blots, we found the protein level of Trem2 to be reduced by approximately 60% in brain homogenates. This correlates with RNA-sequencing results. PET imaging using 64Cu-PTSM and 19F-FDG shows a reduction in glucose metabolism of mice at older ages. Despite the reduction in messenger RNA, there is significant full-length expression of mutant Trem2 mRNA in mice carrying the Trem2*R47H variant. This is consistent with the reduction in Trem2 protein is observed from brains. Furthermore, this model does not phenocopy a Trem2 knockout since significant expression of Trem2 protein in brain tissue is observed and transcriptome alterations are different and less pronounced. In addition, these mice may show a potential perfusion-metabolism pattern that is different than wild-type mice. Future studies with these models aid in understanding how Trem2 plays a role in the progression of AD.

Disclosures: A.L. Oblak: None. **H. Williams:** None. **K. Kotredes:** None. **M. Sasner:** None. **S.J. Sukoff Rizzo:** None. **G. Carter:** None. **G.R. Howell:** None. **C. Preuss:** None. **A. Uyar:** None. **R.S. Pandy:** None. **C. Ingraham:** None. **D. Soni:** None. **V. Jadhav:** None. **A.P. Tsai:** None. **P.R. Territo:** None. **B. Logsdon:** None. **B.T. Lamb:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.07/E26

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

Support: 5U54AG054349-02

Title: Comparative transcriptome analysis of MODEL-AD mouse models

Authors: *G. BALDERRAMA-GUTIERREZ[1], A. MORTAZAVI[1], M. AD CONSORTIUM[2,3,4,5];
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Abstract: Alzheimer’s disease (AD) is a neurodegenerative pathology characterized by the loss of memory and cognitive impairment. Accumulation of amyloid-βplaques and tangles are key pathological signatures that are associated with the disease. Existing mouse models of AD are based on familial mutations that lead to an early onset of the disease. MODEL-AD is tasked to develop novel models that are more representative of the late onset version of the disease. The consortium is collecting RNA-seq datasets from cortex and hippocampus in a time course of neurodegeneration in both AD model mice and wildtype controls as part of the deep phenotyping of these mice. We are also collecting similar time courses from well-established familial mouse models for comparative purposes. Our RNA-seq datasets include a single-cell RNA-seq pilot for a select set of mice. We are analyzing the data for both differential expressed genes and modules that are either common or specific for the different models. As these modules are refined, we are comparing them to results from AMP-AD to identify which of the same genes are turned on during disease progression in human. All data are released through the Synapse portal. As part of the validation of our RNA-seq analysis pipeline, we have analyzed a time course of gene expression in hippocampus and cortex of 5xFAD mice at 4, 8 and 12 months. We recover, as expected, a strong inflammatory module that is more pronounced in females. While many of the inflammatory module genes peak at 8 months, we see a subset of genes such as members the complement system that continue to increase at 12 months in hippocampus. We are investigating whether the same gene expression profiles are consistent in other mouse models as they are characterized in our phenotypic pipeline as well as compared to human AD modules.

Disclosures: G. Balderrama-Gutierrez: None. **A. Mortazavi:** None. **M. AD Consortium:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.08/E27

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

Support: 7AZ10 for the Ed and Ethel Moore Alzheimer's Disease Research Program
NINDS 1 F30 NS105408-01

Title: Modulation of corticotropin releasing factor (CRF) in a CRND8 mouse model of Alzheimer disease-like amyloidosis improves spatial navigation in the water maze test

Authors: *C. G. JANUS, G. GIRALDO, H. S. FUTCH, T. E. GOLDE;
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Abstract: Chronic psychological stress affects the stress-responsive corticotropin-releasing factor (CRF) and glucocorticoid (GC) signaling systems that are putative targets in neuropsychiatric, cardiovascular, and neurodegenerative diseases. The presence of elevated cortisol levels in Alzheimer disease (AD) patients supports the hypothesis that stress may contribute to the severity of AD. Since stress is also associated with hippocampal damage and impaired memory, we hypothesized that the modulation of CRF activity might mitigate associated comorbidities of anxiety or agitation, ameliorating cognitive function. To this end, we developed a high affinity monoclonal antibody (CTRND05) targeting CRF. In mice, CTRND05 blocks stress-induced increases in corticosterone, and induces phenotypes consistent with suppression of the HPA axis. In this preliminary study, we used the CRND8 mouse model of AD-like amyloidosis. The mice were immunized against CRF for 3 months, starting at 3 months of age with the onset of amyloid deposition in the brain. Two CRND8 transgenic (Tg) groups, immunized against CRF (anti-CRF, n = 11) and immunized with IgG (n = 9), and a group of naïve non-transgenic (nTg) littermates (n = 16) were used. Groups were closely sex balanced. The mice were evaluated at 6 months of age in the SHIRPA screen, followed by the Light/Dark (LD) anxiety test and the spatial reference memory version of the Morris water maze (MWM) test. No differences were found in the physical condition and reflexes between the groups (SHIRPA screen). Although the LD test did not reveal changes in the anxiety of CRND8 mice, the immunization against CRF reduced hyperactivity previously observed in this model. The IgG mice, however, showed characteristic locomotor hyperactivity in the test. The analysis of the search path during learning acquisition in the MWM revealed significant treatment ($p = 0.003$) and treatment by training day ($p = 0.040$) effects. The anti-CRF mice showed comparable search paths to nTg mice ($p = 0.14$), while the paths of IgG mice were longer ($p = 0.02$, Dunnett t, 2-sided test). The improvement in performance of anti-CRF mice was substantiated by the analysis of the latencies to reach the vicinity of the escape platform (annulus of 2 X the platform diameter). Anti-CRF and nTg mice showed short and comparable latencies to the annulus area ($p = 0.78$), that were different from the latencies of IgG mice ($p = 0.004$ and $p < 0.001$, respectively). However, these differences were not reflected in the probe trial test. In conclusion, our results indicate that 3-month long passive immunization against CRF improved the “knowing where” aspect of spatial navigation in CRND8 mice in MWM.

Disclosures: **C.G. Janus:** None. **G. Giraldo:** None. **H.S. Futch:** None. **T.E. Golde:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.09/E28

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

Support: NIH Grant AG045031
NIH Grant AG059195
NIH Grant AG057768
NIH Grant AG056901

Title: Perinatal choline supplementation normalizes spatial learning and memory deficits in the APP.PS1 Alzheimer's disease model mice

Authors: T. J. MELLOTT, E. M. BRUNS, K. N. CORDEIRO, N. WASIF, A. P. SANKAR, *J. K. BLUSZTAJN;
Pathology and Lab. Med., Boston Univ. Sch. of Med., Boston, MA

Abstract: Prevention of Alzheimer's disease (AD) is a major goal of biomedical sciences. In previous studies we showed that high intake of the essential nutrient, choline, during gestation prevented age-related memory decline in a rat model. We also reported (Mellott et al, PMID:28103298) that the hippocampus of perinatally choline-supplemented AD model APP.PS1 (MGI ID: 3524957) mice exhibited: 1) reduced number and total area of amyloid plaques; 2) preserved levels of choline acetyltransferase and insulin-like growth factor II proteins; and 3) absence of astrogliosis, as compared to APP.PS1 mice reared on control diet. In this study we tested the hypothesis that perinatal choline supplementation ameliorates the cognitive impairment in this model of AD. We placed wild type (WT) females and hemizygous APP.PS1males on the control AIN76A diet (1.1 g/kg of choline chloride) or on a choline-supplemented AIN76A diet (5 g/kg of choline chloride). After 7 days, the animals were mated and the dams continued to consume their prenatal diets through birth and lactation until weaning of the pups on postnatal day 21. Subsequently all offspring consumed the control diet. Learning and memory of the animals of both sexes were assessed in a Barnes maze at 6 and 9 months of age. All animals learned the task. At 6 months of age there were no differences between the experimental groups. At 9 months of age the APP.PS1 mice whose mothers consumed the control diet were impaired requiring 47% longer time to locate the escape pod in the maze at the final trial of training as compared to the WT mice ($p=0.03$). However, the behavior of APP.PS1 mice whose mothers consumed the choline-supplemented diet was ameliorated, resembling that of the WT animals. Perinatal choline supplementation had no effect on the behavior of the WT mice. The results are consistent with a recent report by Velazquez et al (PMID:30622336).

Overall, these data suggest that dietary supplementation with choline during early life may constitute a preventive strategy for AD.

Disclosures: T.J. Mellott: None. **E.M. Bruns:** None. **K.N. Cordeiro:** None. **N. Wasif:** None. **A.P. Sankar:** None. **J.K. Blusztajn:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.10/E29

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

Support: NIA U54 AG05434503

Title: Transcriptomic analysis of chronic levetiracetam treatment in aged 5XFAD mice: Relationship with pharmacokinetics and pharmacodynamics

Authors: *S. J. SUKOFF RIZZO[1], K. D. ONOS[2], K. KEEZER[3], L. HAYNES[3], H. WILLIAMS[3], S. K. QUINNEY[4], A. MASTERS[4], C. BIESDORF DE ALMEIDA[4], A. A. BEDWELL[4], J. A. MEYER[5], C. INGRAHAM[6], J. PETERS[4], S. A. PERSOHN[4], R. SPEEDY[4], L. FIGUEIREDO[4], K. ELDRIDGE[4], M. SASNER[3], A. OBLAK[6], B. T. LAMB[6], G. CARTER[3], P. R. TERRITO[5];
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Abstract: The Preclinical Testing Core (PTC) of the Model Organism Development for Late Onset Alzheimer’s Disease (MODEL-AD) consortium has established a streamlined preclinical drug testing strategy with go/no-go decision points that allow critical and unbiased assessments of potential therapeutic agents. For the present studies, we selected levetiracetam (LEV), a compound currently in clinical trials for the treatment of cognitive impairment associated with AD, for testing in 5XFAD mice. Initial pharmacokinetics (PK) analysis revealed a short half-life of LEV requiring twice daily dosing. Chronic administration of LEV (veh, 10, 30, and 56 mg/kg, p.o., BID). began at 3 mos. of age, prior to the onset of significant amyloid load in 5XFAD mice with all pharmacodynamics (PD) endpoints measured at 6 mos. of age in male and female 5XFAD mice and vehicle-treated age-and sex-matched WT controls (n=11-20 per sex/genotype/treatment) and included: 18-FDG PET/MR, 18F-AV45 PET/MR, autoradiography, immunohistochemistry, spontaneous alternation, open field activity, rotarod, PK analysis, and gene expression profiling using the Nanostring nCounter Mouse AD Panel, which includes a set of 770 genes prioritized for probe design by MODEL-AD that includes coverage of all AD-associated modules from AMP-AD clinical samples with human-mouse homology. In line with

the ARRIVE guidelines, all technicians were blinded to dose and genotype during execution of experiments and throughout data collection and analysis, with all samples and subjects randomized and counterbalanced. Prophylactic treatment with LEV produced dose-related alterations in behaviors related to activity without significant improvements on cognitive performance. LEV also failed to alter amyloid deposition as measured by 18F-AV45 PET or alterations of glucose uptake as measured by 18-FDG PET. Transcriptomic analysis revealed expected gene expression profile changes related to AD in male and female 5XFAD mice relative to age-matched WT controls. LEV treatment resulted in correlations with gene expression modules related to neuron and glial development, and myelination, and anti-correlated with gene expression modules related to synaptic signaling and nervous system development which were mildly dose-related and in some cases sex-dependent. Taken together these data indicate that the 5XFAD mouse model may not be an optimal model for evaluating the PD effects of LEV, however transcriptomic analysis revealed suggestive evidence that LEV ameliorates some of the synaptic damage from the transgene while intensifying the myelination defects related to AD; findings which require further investigation.

Disclosures: **S.J. Sukoff Rizzo:** None. **K.D. Onos:** None. **K. Keezer:** None. **L. Haynes:** None. **H. Williams:** None. **S.K. Quinney:** None. **A. Masters:** None. **C. Biesdorf De Almeida:** None. **A.A. Bedwell:** None. **J.A. Meyer:** None. **C. Ingraham:** None. **J. Peters:** None. **S.A. Persohn:** None. **R. Speedy:** None. **L. Figueiredo:** None. **K. Eldridge:** None. **M. Sasner:** None. **A. Oblak:** None. **B.T. Lamb:** None. **G. Carter:** None. **P.R. Territo:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.11/E30

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

Support: Emerald Foundation, Inc grants to Charbel E-H Moussa

Title: Ubiquitin specific protease 13 regulates tau accumulation and clearance in models of Alzheimer’s disease

Authors: *X. LIU, M. HEBRON, S. MULKI, C. WANG, E. LEKAH, D. FERRANTE, W. SHI, B. KURD-MISTO, C. MOUSSA;
Georgetown Univ. Med. Ctr., Washington DC, DC

Abstract: Background: Ubiquitin Specific Protease-13 (USP13) is a de-ubiquinating enzyme that regulates protein ubiquitination and clearance. The role of USP13 is largely unknown in neurodegeneration. In this study we aim to demonstrate whether tau accumulation and/or clearance depends on ubiquitination/de-ubiquitination via USP-13. **Methods:** We used

transgenic animal models of human amyloid precursor protein (APP) or P301L tau mutations and genetically knocked-down USP13 expression via shRNA to determine USP13 effects on tau ubiquitination and levels. **Results:** We found a two-fold increase of USP13 levels in post-mortem Alzheimer's disease (AD) brains. USP13 knockdown significantly increased the activity of the 20S proteasome and reduced the levels of hyper-phosphorylated tau (p-tau) in primary cortical neurons. USP13 knockdown also reduced the levels of amyloid plaques and increased p-tau ubiquitination and clearance in transgenic animal models that over-express murine tau as a result of the expression of familial APP mutations (TgAPP) and the human mutant P301L tau (rTg4510), respectively. Clearance of p-tau appears to be mediated by autophagy in these animal models. **Conclusions:** Taken together, these data suggest that USP13 knockdown reduces p-tau accumulation via regulation of ubiquitination/de-ubiquitination and mediates its clearance via autophagy and/or the proteasome. These results suggest that USP13 inhibition may be a therapeutic strategy to reduce accumulation of plaques and toxic p-tau in AD and human tauopathies. **Keywords:** USP13, Tau, Ubiquitin, Amyloid, Alzheimer's disease

Disclosures: X. Liu: None. **M. Hebron:** None. **S. Mulki:** None. **C. Wang:** None. **E. Lekah:** None. **D. Ferrante:** None. **W. Shi:** None. **B. Kurd-Misto:** None. **C. Moussa:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Charbel Moussa is an inventor on issued US Georgetown University patents to use USP13 inhibitors as a treatment for neurodegenerative diseases..

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.12/E31

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

Support: NIH AG045656 MH083911
Alzheimer's Association

Title: Gene therapy-based cell therapy for neural regeneration and repair

Authors: *G. CHEN, Z. WU, X. HOU, Z. GUO, Y. CHEN, J. YIN, N. MA, L. ZHANG; Biol., Penn State Univ., University Park, PA

Abstract: There are huge unmet medical needs to treat severe neurological disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, stroke, spinal cord injury, ALS, and many more. Neuronal loss is the major cause of functional deficits observed in Alzheimer's disease patients, yet adult human brain has largely lost the neuroregeneration capability in most regions. Regenerating millions or even billions of functional new neurons to replenish the lost neurons is critical to restore impaired learning and memory capacity among Alzheimer's disease

patients. We have recently developed an innovative *in vivo* cell conversion technology to directly convert reactive glial cells into functional new neurons inside adult mouse brains through expressing a single neural transcription factor NeuroD1 (Guo et al., Cell Stem Cell). Using AAV-based gene therapy, we demonstrate that our astrocyte-to-neuron conversion technology can regenerate not only a large number of functional new neurons but also can protect a significant number of injured neurons. Therefore, we are developing an innovative gene therapy-based cell therapy to treat neurodegenerative disorders such as Alzheimer's disease. Moreover, after high efficiency NeuroD1-mediated *in vivo* astrocyte-to-neuron conversion, the remaining astrocytes can proliferate and replenish themselves, accompanied with reduced neuroinflammation and increased angiogenesis. The NeuroD1-converted neurons are highly functional, showing repetitive action potentials and robust synaptic activities, and sending out long-range axonal projections to global brain targets. Together, these results demonstrate that in vivo astrocyte-to-neuron conversion technology shows a great potential in the treatment of neurodegenerative disorders through regeneration of new neural tissue consisted of new neurons, new astrocytes, and new blood vessels.

Disclosures: **G. Chen:** Other; Co-founder of NeuExcell. **Z. Wu:** None. **X. Hou:** None. **Z. Guo:** None. **Y. Chen:** None. **J. Yin:** None. **N. Ma:** None. **L. Zhang:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.13/E32

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

Support: ZonMw grant nr. 733050106

Title: Learning-induced transcription factor Egr1 as a candidate for gene therapy in Alzheimer's disease

Authors: *S. UYANIKER[1], B. HOBO[1], S. VAN DER SPEK[2], K. BOSSERS[1], F. DE WINTER[1], A. B. SMIT[2], H. W. KESSELS[3], J. VERHAAGEN[1];
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Abstract: A major hallmark of Alzheimer’s disease is dysfunction and loss of synapses due to an excess of amyloid beta (Aβ). Interestingly, individual susceptibility to Aβ synaptotoxicity seems to exist. In particular, mental exercise is thought to delay the onset of Alzheimer’s disease. Our data from the human Alzheimer’s disease brain suggest that the learning-induced

transcription factor Egr1 may play an instrumental role in protecting neurons against Aβ. We found that Egr1, and many synaptic genes that are regulated by Egr1, are increased in the earliest stages of the disease, when Aβ already accumulates but memory is largely intact (Braak 0-II). In later, stages of Alzheimer's disease, there is a significant decline in Egr1 expression and its target genes (Braak III-VI). To directly assess the effects of Egr1 on synaptic function in neurons, we used viral vectors to simultaneously overexpress Egr1 and APP-CT100 (the precursor to Aβ) in cultured hippocampal slices. We measured synaptic transmission using whole-cell patch clamp recordings, and dendritic spine densities using two-photon microscopy. Furthermore, we studied the effects of viral vector-mediated hippocampal Egr1 overexpression on the transcriptome, synaptic proteome and discrimination and reversal learning behavior in an APP/PS1 mouse model. Our data suggest that Egr1 overexpression might render synapses less susceptible to Aβ-induced synaptic weakening and loss of synapses, induce changes in the transcriptome and synaptic proteome, and counteract the effects of the APP/PS1 genotype on discrimination learning, underlining its potential as a tool for gene therapy in early Alzheimer's disease.

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Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.14/E33

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

Support: NIH Grant R01NS082283
Lundin Foundation
Sebastian Velona Foundation

Title: Analyzing sex-dependent differences in disease progression in mouse models of CLN3 and CLN8 Batten disease

Authors: ***B. L. MEYERINK**, Z. P. ZENNER, K. A. WHITE, T. B. JOHNSON, S. S. DAVIS, C. SWANSON, C. D. BOOTH, L. A. LANGIN, M. A. PRATT, K. J. TIMM, J. T. CAIN, J. M. WEIMER;
Pediatrics and Rare Dis. Group, Sanford Res., Sioux Falls, SD

Abstract: Batten disease is a group of rare pediatric neurodegenerative disorders characterized pathologically by the accumulation of lysosomal storage material, neuronal death, and glial activation. Clinical features include loss of motor coordination and cognitive function, retinopathies leading to blindness, seizures, and premature death. Clinical data suggests a sex-

linked variation in the onset and progression of these disorders yet traditional use of animal models of these disorders neglect to consider sex as a significant factor in disease characteristics. In this study, we examine sex-based disease differences in *Cln3*$^{\Delta ex7/8}$ and *Cln8*^{mnd} mouse models of Batten disease. To track disease progression, we use the classical histopathological markers of glial activation, astrocytosis, and accumulation of storage material. Additionally, we use a battery of behavioral assays to examine learning and memory, motor function, and mobility. Differences in disease parameters show evidence that sex influences the progression of the disease in certain forms of Batten disease. Pathology analyzed in this study is based on tissue collection that would be impractically invasive in humans and further characterizes the sex-determined differences in these disorders. Our data indicate a need for consideration of sex-based variability in disease presentation when using research models, assessing therapies in clinical trials, and tracking progression of Batten disease in the clinical setting.

Disclosures: B.L. Meyerink: None. **Z.P. Zenner:** None. **K.A. White:** None. **T.B. Johnson:** None. **S.S. Davis:** None. **C. Swanson:** None. **C.D. Booth:** None. **L.A. Langin:** None. **M.A. Pratt:** None. **K.J. Timm:** None. **J.T. Cain:** None. **J.M. Weimer:** None.

Poster

473. Alzheimer's Disease and Other Dementias: Therapeutic Strategies II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 473.15/E34

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

Support: Lundin Foundation
NIH R01NS082283
NIH P20GM103620

Title: Intrathecal scAAV9-CLN3 administration rescues pathological and behavioral deficits and prolongs survival in a preclinical model of Batten disease

Authors: *M. A. PRATT[1], T. B. JOHNSON[2], S. LIKHITE[4], J. T. CAIN[2], K. A. WHITE[2], D. TIMM[2], B. L. MEYERINK[2], S. DAVIS[2], R. H. PINEDA[5], C. DENNYS-RIVERS[4], K. C. MEYER[6], J. M. WEIMER[3];
[1]Weimer Lab., [3]Children's Hlth. Res. Ctr., [2]Sanford Res., Sioux Falls, SD; [4]Nationwide Children's Hosp., Columbus, OH; [5]Surgery/ Urology Res., Univ. of Colorado Sch. of Med., Aurora, CO; [6]Ctr. for Genetherapy, Res. Inst. Nationwide Childrens Hosp., Columbus, OH

Abstract: Mutations in the CLN3 gene cause CLN3-Batten disease (also called juvenile neuronal ceroid liposfuscinosis; JNCL), which is a severe neurodegenerative disorder leading to dementia, epilepsy, motor impairment, and visual degradation. The disease onset varies between 4-7 years of age, but the outcome is fatal in all cases, leading to death between 20-30 years of

age. To date, the function of the CLN3 protein is poorly understood, but mutations disturb the lysosomal storage clearance process. Since CLN3 mutations found in patients predominantly cause reduced abundance or functionality of the protein, strategies to increase levels of functional protein are considered highly promising for therapy. In the current study, we evaluate the therapeutic efficacy of Adeno-Associated virus Serotype 9 mediated delivery of functional CLN3 in a mouse model carrying the most frequent human mutation, *CLN3*$^{\Delta ex7/8}$. We show that a single, intrathecal administration of scAAV9.CLN3 at postnatal day 1 results in robust and widespread expression of CLN3 throughout the brain and spinal cord of *CLN3*$^{\Delta ex7/8}$ mice. scAAV9.CLN3 treatment ameliorates the pathological hallmarks of CLN3-Batten disease such as accumulation of autofluorescent storage material (ASM), as well as ATP synthase subunit C in various regions of the central nervous system in *CLN3*$^{\Delta ex7/8}$ mice. This is also accompanied by a significant reduction in glial activation. More importantly, the therapeutic effects of scAAV9.CLN3 administration persists throughout the lifespan of the treated mice. Along with the histopathological improvement, scAAV9.CLN3 treatment also demonstrates motor and cognitive improvements in *CLN3*$^{\Delta ex7/8}$ mice as assessed by pole climbing assay, rotarod analysis and Morris water maze test. Additionally, intrathecal administration of scAAV9.CLN3 in non-human primates results in widespread expression of CLN3 throughout the central nervous system and is safe and well-tolerated up to 6 months post-injection. Altogether, these data underline that intrathecal administration of scAAV9.CLN3 is a promising therapeutic strategy for CLN3-Batten Disease.

Disclosures: **M.A. Pratt:** None. **T.B. Johnson:** None. **K.A. White:** None. **S. Likhite:** None. **J.T. Cain:** None. **B.L. Meyerink:** None. **D. Timm:** None. **S. Davis:** None. **J.M. Weimer:** None. **R.H. Pineda:** None. **K.C. Meyer:** None. **C. Dennys-Rivers:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.01/E35

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Genomic screening for the identification of putative molecular targets involved in HTT modulation in hESC

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Abstract: Despite exciting progress made in clinical trials for treatment of Huntington's disease (HD), the delivery and distribution of large nucleic acid molecules throughout all compartments of the brain remains challenging. Identification of targets that modulate (mutant) HTT levels to which small molecules can be designed can potentially achieve the same result of lowering mHTT levels, but would be superior in terms of distribution and delivery methods. To this end, a total of ~70,000 individual siRNA sequences (four siRNAs per target) were screened in HD human embryonic stem cells (hESC) to identify potential targets for mHTT modulation. Hit selection resulted in 4560 siRNAs which were then counter screened for cytotoxic effects.
For robust determination and elimination of hits that exert their effect on mHTT levels through adverse cellular effects, three different toxicity assays, i.e. RealTime-Glo™, propidium-iodide based high-content image analysis and AKT HTRF were multiplexed together with mHTT HTRF, the primary readout. All QC measures were satisfactory with significant assay windows to select non-toxic candidates. To identify a cut off selection, the results obtained in each assay were ranked, summed and combined with effects on mHTT levels. This resulted in 435 putative non-toxic genes inhibiting mHTT levels, of which 51 genes were targeted by two or more siRNA. Together with one gene that increased mHTT levels when targeted by multiple siRNAs, a total of 52 targets are prioritized in a tier one target validation approach.
With the elimination of targets that upon silencing induced toxicity, a tier one list of candidate genes are being evaluated to determine on-target knockdown efficiency and their corresponding effect on *HTT* mRNA. The downstream cascade to further validate the putative molecular targets, are underway.

Disclosures: **D.F. Fischer:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Charles River. **M. Atalar:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **L. van Beek:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **L. Bishop-Currey:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **H. Li:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **Z. Day:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **M. Fokkelman:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **A. Zuurmond:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **J. DeGroot:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **P. Mitchell:** A. Employment/Salary (full or part-time):; Charles River. 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.; Charles River on behalf of CHDI. **J. Greene:** A. Employment/Salary (full or part-time):; Rancho Biosciences. 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.; Rancho Biosciences on behalf of CHDI. **G. McAllister:** A. Employment/Salary (full or part-time):; CHDI Foundation. **D. Macdonald:** A. Employment/Salary (full or part-time):; CHDI Foundation. **C. Dominguez:** A. Employment/Salary (full or part-time):; CHDI Foundation. **T.F. Vogt:** A. Employment/Salary (full or part-time):; CHDI Foundation. **I. Munoz-Sanjuan:** A. Employment/Salary (full or part-time):; CHDI Foundation. **S. Jang:** A. Employment/Salary (full or part-time):; CHDI Foundation.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.02/E36

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: ANR-12-EMMA-0013
ANR-14-CE13–0035

Title: Rescue of BDNF/TrkB pathway in Huntington's disease models by a Huntingtin domain: P42

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Abstract: Huntington's disease (HD) is a fatal genetic neurodegenerative disorder with no curative treatment yet available. This disorder is due to a mutation in the *HTT* gene which encodes for the Huntingtin protein (Htt). In HD, expression of mutant Htt (mHtt) carrying extended polyQ domain leads to important dysfunction of the BDNF/TrkB signalling pathway. Indeed, in HD there are issues in the production of BDNF, its transport and also on the level of the BDNF receptor: TrkB. P42, a 23aa peptide isolated from Htt, was found to prevent pathological phenotypes induced by mHtt. More specifically, in HD conditions , P42 is able to protect from mhtt aggregation, axonal transport defects and impaired neuronal viability. The aim of our study was to better understand P42 mechanism of action in order to increase its therapeutic potential. In this study we focused on the effect of P42 on BDNF/TrkB pathway. To do so, first we observed the impact of a P42 treatment on BDNF/TrkB associated phenotype in R6/2 mouse model of HD. Mainly, we found that P42 rescues TrkB protein level in the striatum but also restores BDNF transcript level in the cortex. Then we observed that P42 treatment is able to increase BDNF/TrkB associated behaviours such as memory, anxiety and motor coordination affected in R6/2 mice. Using electrophysiological approach we also noticed a significant effect of P42 on neuronal plasticity, which is also BDNF/TrkB dependant. Furthermore, using environmental enrichment through the Hamlet test, we observed that increasing the BDNF expression could have a synergic effect with P42, explained by an effect of P42 at different levels of the BDNF/TrkB pathway. To investigate this question, we analysed the transport of the *Drosophila* BDNF homolog (DNT1) in neurons. We noticed that the expression of P42 is able to decrease pathological phenotype induced on DNT1 transport by the expression of mHtt. All these results suggest that P42 may have an action on BDNF/TrkB pathway through an effect on BDNF transport, additionally to its effect on TrkB protein level.

Disclosures: S. Couly: None. **A. Carles:** None. **T. Maurice:** None. **F. Maschat:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.03/E37

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH Grant NS098772

Title: Mutant Huntingtin does not acutely damage brain mitochondria

Authors: *J. HAMILTON[1], T. BRUSTOVETSKY[1], N. BRUSTOVETSKY[1,2];
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Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disorder, characterized by severe motor and cognitive abnormalities, that is linked to a mutation in the ubiquitously expressed huntingtin protein (Htt). Although the mechanisms by which mutant huntingtin (mHtt) induces HD remain incompletely understood, defects in mitochondrial bioenergetics and Ca^{2+} handling have been implicated. The mechanism of deleterious mHtt action could include transcriptional alterations, direct physical interaction with mitochondria, or a combination of these factors. In the present study, we tested the hypothesis that mHtt directly and acutely impairs mitochondria. To test this hypothesis, we treated brain mitochondria from wild-type (WT) mice with mHtt-containing brain cytosolic fraction from YAC128 mice, an HD mouse model, and assessed mitochondrial respiration, membrane potential, ROS production, and Ca^{2+} uptake capacity. The amount of mHtt bound to WT mitochondria following incubation with mHtt-containing cytosolic fraction was greater than the amount of mHtt bound to brain mitochondria isolated from YAC128 mice. However, despite mHtt binding to mitochondria, no abnormalities were detected in any of the tested mitochondrial functions. This is consistent with the results produced in our previous studies, which provided no evidence for defects in isolated, purified brain mitochondria from R6/2 and YAC128 mice (1-4). In addition to experiments with WT mitochondria, we performed experiments in which we augmented the amount of mHtt bound to mitochondria from HD mice by incubating brain mitochondria isolated from YAC128 mice with mHtt-containing cytosolic fraction. Despite enrichment of YAC128 brain mitochondria with mHtt, mitochondrial functions (respiration, membrane potential, ROS production, Ca^{2+} uptake capacity) remained unchanged. Overall, our results suggest that mHtt does not directly and acutely impair mitochondrial functions, arguing against the involvement of this mechanism in HD.
1. Pellman, J.J., et al. (2015) *J. Neurochem.* 134, 652-667.
2. Hamilton, J., et al. (2015) *Hum. Mol. Gen.* 24, 4862-4878.
3. Hamilton, J., et al. (2016) *Hum. Mol. Gen.* 25, 2762-2775.
4. Hamilton, J., et al. (2017) *Neurochemistry International* 109, 24-33.

Disclosures: J. Hamilton: None. **T. Brustovetsky:** None. **N. Brustovetsky:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.04/E38

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Investigating the role of aging in Huntington disease pathogenesis

Authors: *E. MACHIELA[1], M. SCHMIDT[2], M. R. HAYDEN[3], V. B. MATTIS[4], A. SOUTHWELL[1];
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Abstract: Huntington disease (HD) is an autosomal dominant disease caused by a CAG repeat expansion in exon 1 of the huntingtin gene. HD is characterized by loss of voluntary movement, neuropsychiatric abnormalities, and cognitive decline. There are currently no disease-modifying therapies for HD. While age of onset negatively correlates with CAG repeat tract length, this only accounts for some of the variation in onset age observed in HD patients; many other genetic and environmental factors play a role in disease onset. Carriers of the mutation that causes HD can live asymptomatically until mid-life, begging the question of how the aging process may contribute to onset of disease. Accelerated markers of aging and cellular functions that decline during the aging process, such as the stress response and functions of the proteasome and mitochondria undergo rapid decline in HD, further supporting the hypothesis that aging contributes to HD pathology. To investigate the role of aging in HD, we are using induced pluripotent stem cell (iPSC)-derived neurons from HD patients as well as healthy controls. iPSC-derived adult-onset HD neurons exhibit very mild phenotypes and no spontaneous neurodegeneration. To overcome this, we treated HD and control cells with progerin, a truncated protein created by alternative splicing of the LMNA gene. Accumulation of progerin causes Hutchinson-Gilford progeria, a disease of rapid aging. Progerin has also been found in healthy tissues during the aging process and has been linked to cellular senescence. In doing this, we can compare cellular phenotypes in HD neurons that are physiologically “young” and “old” but chronologically identical, to determine the role of physiologic aging in the cellular toxicity of HD. Ultimately, this work will shed light on aging-associated factors that contribute to HD pathogenesis and whether anti-aging treatments may be beneficial for HD patients.

Disclosures: E. Machiela: None. **A. Southwell:** None. **M. Schmidt:** None. **M.R. Hayden:** None. **V.B. Mattis:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.05/E39

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Sensitive mRNA expression quantification by ViewRNA for high-throughput screening in human Huntington’s disease embryonic stem cells

Authors: M. VISSER[1], G. SERVANT[1], E. THATCHER[2], D. DUINSBERGEN[1], N. DE JONG[1], *F. VERKAAR[1], M. VROUWE[1], **A.-M. ZUURMOND**[1], J. DEGROOT[1], D. F. FISCHER[2], P. MITCHELL[2], R. Z. CHEN[3], G. MCALLISTER[3], T. F. VOGT[4], C. DOMINGUEZ[4], I. MUNOZ-SANJUAN[4];
[1]Charles River, Leiden, Netherlands; [2]Charles River, Saffron Walden, United Kingdom; [3]CHDI Mgmt., New York, NY; [4]CHDI Mgmt., Los Angeles, CA

Abstract: Targeting *HTT* mRNA is showing promising results in a Phase 1/2 trial in Huntington's disease (HD) patients, while targeting an RNA splicing mechanism proved to lower HTT protein levels in an HD animal model. This indicates that (mutant) *HTT* mRNA can be considered as an important therapeutic target for HD. Phenotypic screening efforts focusing on *HTT* mRNA as target require a robust and high-throughput assay.
Here we aim to develop a highly sensitive ViewRNA assay able to detect total and allele-specific *HTT* mRNA levels in human embryonic stem cells (hESC) and in hESC-derived neurons. Using a probe set targeting *HTT* exons 42-47, we observed siRNA-mediated depletion of *HTT* mRNA in GEN020 hESCs, which was confirmed on the protein level. PTC compound-mediated knockdown of *HTT* mRNA demonstrated a concentration-dependent response as detected by ViewRNA and confirmed by RT-qPCR. To detect allele-specific *HTT* mRNA we barcoded *HTT* exon 12 *in silico* by introducing silent mutations. Specificity of the probe sets designed for wild-type (wt)*HTT* exon 12 and the barcoded (bc) version was confirmed in GEN020 hESC transiently expressing either wt or bc *HTT* exon 12 mRNA. Moreover, endogenous *HTT* mRNA levels were only detected with the wt exon 12 probe set. Although this probe set targets a significantly smaller region within *HTT* than the exon 42-47 probe set, similar siRNA and compound-mediated *HTT* mRNA depletion was detected for this custom-designed probe set. Taken together, we demonstrated that total and allele-specific *HTT* mRNA expression levels can be robustly detected using ViewRNA technology in hESCs. Our future efforts focus on further optimization of the ViewRNA protocol for high-throughput assays and transferring these assays from hESCs to hESC-derived neurons. Barcoding of exon 12 by gene editing is performed to generate a hESC line to be able to screen for endogenous *HTT* mRNA modulation in an allele-specific manner.

Disclosures: M. Visser: None. **G. Servant:** None. **E. Thatcher:** None. **D. Duinsbergen:** None. **N. de Jong:** None. **F. Verkaar:** None. **M. Vrouwe:** None. **A. Zuurmond:** None. **J. DeGroot:** None. **D.F. Fischer:** None. **P. Mitchell:** None. **R.Z. Chen:** None. **G. McAllister:** None. **T.F. Vogt:** None. **C. Dominguez:** None. **I. Munoz-Sanjuan:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.06/E40

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: A phenotypic high throughput screen for Huntingtin lowering small molecules in Huntington's disease patient fibroblast cells

Authors: *L. M. S. STANEK[1], S. MUELLER[4], C. LAFON[4], A. ROTH[5], A. GRABBE[5], N. MICHAELSEN[5], A. SCHLUETER[5], M. VARBAN[2], S. EYQUEM[3], F. MARGUET[3], L. S. SHIHABUDDIN[1], R. GODEMANN[5];
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Abstract: Huntington's disease (HD) is a neurological disorder caused by mutations in the huntingtin (HTT) gene, the product of which leads to selective and progressive neuronal cell death in the striatum and cortex. Lowering of the pathogenic mutant huntingtin (mHTT) protein is the most proximal approach to treating this devastating disease. A number of HTT lowering therapies such as AAV-RNA interference (RNAi) and antisense oligonucleotides (ASOs) are in development but invasive delivery methods and relatively poor CNS distribution still remain a challenge. A brain penetrant small molecule that lowers HTT would provide the advantage of oral dosing and systemic distribution. In an attempt to identify novel compounds that reduce mHTT levels, we have developed a phenotypic high-throughput time-resolved fluorescence resonance energy transfer (TR-FRET) assay for quantification of soluble mutant huntingtin in Huntington's Disease patient fibroblast cells. A high throughput screen of over 1 million compounds from the Sanofi compound library was performed. Results from the screen revealed a high hit rate of 1.7% and a confirmation rate of 49% at 10uM. Hit compounds were then tested in concentration response and triaged for toxicity and huntingtin specificity in orthogonal readouts. Hits demonstrating good separation between mHTT lowering and cytotoxicity will be validated in HD-patient iPSC derived neuronal lines for their ability to reduce neuronal huntingtin protein levels.

Disclosures: **L.M.S. Stanek:** A. Employment/Salary (full or part-time):; Sanofi. **S. Mueller:** A. Employment/Salary (full or part-time):; Evotec. **C. Lafon:** A. Employment/Salary (full or part-time):; Evotec. **A. Roth:** A. Employment/Salary (full or part-time):; Evotec. **A. Grabbe:** A. Employment/Salary (full or part-time):; Evotec. **N. Michaelsen:** A. Employment/Salary (full or part-time):; Evotec. **A. Schlueter:** A. Employment/Salary (full or part-time):; Evotec. **M. Varban:** A. Employment/Salary (full or part-time):; Sanofi. **S. Eyquem:** A. Employment/Salary (full or part-time):; Sanofi. **F. Marguet:** A. Employment/Salary (full or part-time):; Sanofi. **L.S. Shihabuddin:** A. Employment/Salary (full or part-time):; Sanofi. **R. Godemann:** A. Employment/Salary (full or part-time):; Evotec.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.07/E41

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Ministerio de Economia, Industria y Competitividad (SAF2017-88076-R)

Title: Repeated optogenetic stimulation of corticostriatal pathway ameliorates Huntington's disease symptoms

Authors: S. FERNÁNDEZ-GARCÍA[1,2,3], S. CONDE-BERRIOZÁBAL[1,2,4], E. GARCÍA-GARCÍA[1,2,4], G. GARCÍA-DÍAZ BARRIGA[1,2,4], E. RODRÍGUEZ-URGELLÉS[1,2,4], J. LÓPEZ-GIL[2], G. SÒRIA[2], L. CAMPA[5,2,6], F. ARTIGAS[5,2,6], M. J. RODRÍGUEZ[1,2,4], J. ALBERCH[1,2,4], ***M. MASANA**[1,2,4];
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Abstract: Huntington's Disease (HD) is a rare and devastating inherited neurological disorder characterized by motor disturbances including chorea. Brain HD pathology is most prominent in the striatum, with a selective degeneration of GABAergic medium spiny neurons. The cortex is the main afference to the striatum and indeed, there is a progressive disconnection between cortex and striatum manifested as a reduction in striatal synaptic activity. Thus, we aimed to restore motor symptoms by modulating corticostriatal function in symptomatic R6/1 HD mice. We used *in viv*o MRI, optogenetics and microdialysis and *ex vivo* multielectrode arrays to investigate corticostriatal dysfunction in HD. Then, we applied repeated optogenetic stimulation *in vivo* and evaluate motor learning and coordination in R6/1 mice. Structural and functional MRI showed loss of corticostriatal function in R6/1 HD mice. Also, we measured a reduction of striatal glutamate levels (GluCEST and MRS) and corticostriatal release (optogenetics coupled to microdialysis). The electrophysiological response of striatal neurons to optogenetically-induced corticostratal function was also reduced in HD mice (MEA). Finally, repeated corticostriatal optogenetic stimulation in HD mice (R6/1-ChR2) improved motor learning (accelerating rotarod), coordination (balance beam test), exploratory activity (rearings) and stereotypic behavior (grooming), compared to control R6/1-YFP mice, reaching levels similar to WT mice. This improvement was accompanied by an increase in spine density measured using Golgi-Staining. Thus, we demonstrate *in vivo* an effective optogenetic-induced recovery of HD motor

symptoms. Further investigations will help to understand the mechanisms involved and to design novel therapeutic strategies aiming to restore network dysfunction in HD.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.08/E42

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Huntington's Disease Society of America

Title: MicroRNA biogenesis deficits in Huntington's disease

Authors: ***S. PETRY**[1], I. ST-AMOUR[1], C. GOUPIL[1], S. S. HEBERT[2];
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Abstract: BACKGROUND: Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by the expansion of CAG repeats in the exon 1 of the huntingtin gene (HTT). Early transcriptional deregulation is considered to be one of the key events involved in HD pathogenesis. MicroRNA (miRNA) are small non-protein-coding RNAs that regulate gene expression at the post-transcriptional level. Many studies have identified miRNA alterations in HD brain and peripheral system in humans and HD mouse models. Furthermore, miRNA-deficient mice develop HD-related symptoms. Interestingly, we and others have shown that HTT could function in modulating miRNA maturation, strengthening the link between defective miRNA biogenesis and neurodegenerative disorders.
OBJECTIVE: To better understand the role of miRNA biogenesis in HTT-mediated neurodegeneration.
RESULTS: Using Western blot, qRT-PCR and PCR, we analyzed major components of the miRNA biogenesis pathway in a large cohort of human HD brain (cortex and putamen, N=66). This was combined with the analysis of the maturation of selected miRNA species. Consistent with our hypothesis, we observed significant changes in miRNA biogenesis members and miRNA maturation in human AD brain, some of which occurred prior to overt neurodegeneration.
CONCLUSIONS: These data are consistent with a predominant role for miRNA biogenesis alterations as underlying mechanism of miRNA alterations and transcriptional dysregulation

during HD progression. Further investigations are required to delineate the functional relationship between HTT and miRNA biogenesis; more so given the growing interest in gene silencing therapies requiring the endogenous miRNA/RNAi pathway.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

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Program #/Poster #: 474.09/E43

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: NIH NS092525
TL1 TR001415
HD CARE

Title: Potential role of the choroid plexus and cerebrospinal fluid secretion in Huntington's disease pathogenesis

Authors: *I. I. SANCHEZ[1], T. B. NGUYEN[1], W. ENGLAND[1], L. BYRNE[2], R. SPITALE[1], E. WILD[2], E. MONUKI[1], L. M. THOMPSON[1];
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Abstract: Huntington's disease is caused by a CAG repeat expansion mutation in the Huntingtin gene and results in chronic expression of the mutant Huntingtin protein (mHTT), leading to cellular dysfunction, including early and reproducible alterations in gene expression. Cell-to-cell pathology has been implicated in HD and other neurodegenerative diseases, therefore we hypothesize that transcriptional dysregulation in HD may involve both cell intrinsic effects as well as modulation by altered miRNA profiles through exosome secretion via the cerebrospinal fluid (CSF), the majority of which is produced by choroid plexus epithelial cells (CPECs). The aim of this study is to determine whether CSF extracellular vesicles (EVs) from HD patients have altered miRNA profiles that distinguish them from unaffected individuals. To model these potential effects, we are using CPECs differentiated from HD patient-derived induced pluripotent stem cells (iPSCs) to investigate disease phenotypes that might contribute to altered miRNA packaging into EVs. EVs were isolated from HD and unaffected patient CSF samples and nanoparticle tracking analysis used to characterize the CSF EV fraction. miRNA was extracted for QIAseq miRNA sequencing. Our miRNA sequencing studies show that it is feasible to detect specific miRNAs in CSF exosome-enriched EV fractions, and that a subset of HD CSF EV miRNAs may differ in abundance compared to healthy controls. Further, EVs isolated from post-mortem HD CSF contain less of a modified species of the RNA binding protein hnRNPA2B1 compared to healthy control samples. Human iPSCs from juvenile and adult onset HD patients,

and unaffected individuals, were differentiated into CPECs and characterized by qPCR and immunofluorescence. Preliminary studies show primary cilia and tight junction alterations in HD CPECs compared to controls. Our results indicate that miRNA packaging into CSF EVs might be dysregulated in HD, and that a subset of this dysregulation may be a result of hnRNPA2B1 mislocalization and an enhanced cellular stress response. We also show that mHTT expression may have an effect on primary cilia and tight junction formation in iPSC-CPECs, which can potentially have an effect on CSF production and content.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.10/E44

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: The DNAJ proteins DNAJA1 and DNAJB6 modulate polyglutamine aggregation

Authors: *C. HANSEN, C. R. GONZALEZ, S. LIN;
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Abstract: Huntington's disease (HD) is a hereditary neurodegenerative disease caused by CAG repeat expansion in the huntingtin gene, resulting in an expansion of a poly glutamine (polyQ) repeat at the N-terminus of the huntingtin protein. This causes it to abnormally fold and form aggregates resulting in increased neuronal cell death and consequently disease. The DNAJ co-chaperone proteins play a crucial role in transferring misfolded or unfolded proteins to the Hsp70 proteins, which play an essential role for protein folding in the cell. Here, we demonstrate the effect of CRISPR/Cas9-mediated knock out (KO) of individual DNAJ genes on polyQ74 aggregation in HEK293 cells expressing polyQ74 attached to green fluorescent protein (GFP). KO of DNAJB6 resulted in a strong increase in Q74 aggregation whereas KO of DNAJA1 had the opposite effect on polyQ aggregation. KO of DNAJB1 did not change the propensity of polyQ74 to aggregate in cells. These findings where confirmed both by fluorescence microscopy analysis and filter trap assays. DNAJB6KO cells displayed an increased rate of cell death as assessed by tryphan blue exclusion assay, whereas all other KO cell lines did not show more cell death than parental control. These results demonstrates that DNAJ proteins may either act to suppress (DNAJB6) or promote (DNAJA1) polyQ aggregation, and thus that finetuning the cellular levels of DNAJ proteins is critical for suppression of polyQ aggregation and cell survival.

Disclosures: C. Hansen: None. **C.R. Gonzalez:** None. **S. Lin:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.11/F1

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI Foundation (J.B.C.)
Seed Funding/University of Maryland, School of Medicine (S.A.A.)

Title: Huntington's disease transcriptional dysregulation at single-cell resolution

Authors: *M. E. CORTÉS-GUTIÉRREZ[1], S. MALAIYA[1], J. P. CANTLE[2], S. R. LEGG[2], B. R. HERB[1], J. B. CARROLL[2], S. A. AMENT[1];
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Abstract: Neurodegenerative disorders, including Huntington's disease (HD), involve a complex interplay among neurodegenerative and neuroinflammatory processes, yet these cell type-specific mechanisms remain poorly understood. HD is a fatal neurodegenerative disorder characterized by progressive motor, cognitive, and psychiatric symptoms, and caused by dominant inheritance of an expanded trinucleotide (CAG) repeat in the first exon of the *HTT* gene. Among the earliest and most profound neurodegeneration in HD occurs in striatal medium spiny neurons (MSNs), and death of MSNs is thought to explain many of the characteristic features of the disease. Previous studies demonstrated that transcriptional changes are detectable in the striatum long before the onset of cell death. However, the cell type specificity and the trajectory by which individual cells transit from wellness to disease is not known. Here, we characterized cell type-specific transcriptional changes related to HD by sequencing the transcriptomes of >11,000 single-nuclei from whole striatum in a knock-in mouse model of the HD mutation, $Htt^{Q175/+}$, and from wildtype C57BL/6J littermate controls. Our results demonstrate that hundreds to thousands of genes are differentially expressed in each of the major cell types in the striatum, resolving trajectories of transcriptional dysregulation among individual MSNs, revealing HD mutation-associated transcriptional dysregulation in rare cell types, and illuminating the distribution of neuroinflammatory responses across multiple cell types.

Disclosures: M.E. Cortés-Gutiérrez: None. **S. Malaiya:** None. **J.P. Cantle:** None. **S.R. Legg:** None. **B.R. Herb:** None. **J.B. Carroll:** None. **S.A. Ament:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.12/F2

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Analysis of non-coding RNA expression in medium spiny neurons of Huntington's disease model mice

Authors: *H. PARK, H. MIYAZAKI, T. YAMANAKA, N. NUKINA;
Lab. of Structural Neuropathology, Doshisha Univ. Grad. Sch. of Brain Sci., Kyoto, Japan

Abstract: Huntington Disease (HD) is an inherited neurodegenerative disorder with symptoms of movement disorders, psychiatric disturbances and dementia. The disease is caused by expanded CAG repeats encoding polyglutamine in the exon1 of huntingtin gene (*HTT*). In the brains of HD patients, the mutant *HTT* product affects the transcriptional profile of neurons by disrupting the activities of transcriptional machinery which alters the expression of many genes including non-coding(nc) RNAs. Until now, the alterations of ncRNA expression in the brains of both HD patients and model mice have not been fully explored, so we focused on the dysregulation of the expression of ncRNAs.
In this study, from candidate ncRNAs suggested by the gene expression profiling data of MSN in 4-week-old R6/2 HD model mice, we identified dysregulated mouse ncRNAs that have homology with human ncRNAs and are assumed to be highly implicated to HD. By performing real-time PCR, we examined the expression levels of these ncRNAs in the striatum and MSN of R6/2 and control mice. Next, we performed *in situ* hybridization (ISH) on the brains of 4-week-old R6/2 and the control mice to observe the expressions and to examine the localizations of the dysregulated ncRNAs. According to the results, however, unlike coding RNAs, most of ncRNAs either could not be detected clearly by conventional ISH or did not show their expression changes. Therefore, ViewRNA ISH, which provides highly specific signals and more precise detection of RNA, was performed to detect those poorly expressed ncRNAs. Using ViewRNA ISH, we observed the alterations of expression levels and the intracellular localizations of ncRNAs such as *Abhd11os* and *Neat1*. Our study revealed that the expression levels of *Abhd11os* and *Neat1* were altered in MSN of presymptomatic R6/2 mice and the disruption of *Neat1* expression might affect paraspeckle formation, which might be implicated to HD pathogenesis. The roles of ncRNA in neurodegenerative disease have not been fully understood due to their low expression levels. Further research is necessary, but it is expected that ViewRNA ISH will help in investigating the expression changes and understanding the functions of ncRNAs, as well as their implications to the human diseases in the future.

Disclosures: H. Park: None. **H. Miyazaki:** None. **T. Yamanaka:** None. **N. Nukina:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

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Topic: C.04. Movement Disorders other than Parkinson's Disease

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Research Grants Council of Hong Kong, HKUST603/17 to H.P.
Innovation and Technology Commission, ITCPD/17-9 to H.P.

Title: Altered vesicles dynamics in a Huntington's disease mouse model studied with 3D tracking of single synaptic vesicle in cortical neurons

Authors: *S. CHEN[1], X. QIN[2], H. PARK[1];
[1]Div. of Life Sci., Hong Kong Univ. of Sci. and Technol., Hong Kong, Hong Kong; [2]Hong Kong Univ. of Sci. and Technol., Department of Physics, Hong Kong

Abstract: Huntington's disease (HD) is an autosomal dominant genetic disease caused by the abnormal expansion of the cytosine-adenine-guanine (CAG) repeat in huntingtin gene. The major symptoms of HD are progressive motor disorder, cognitive deficits and eventual death. Neuronal death was found initially in the striatum and cortex, and later in other brain regions of HD patients. The altered exocytosis was reported in cortical neurons in a Huntington's disease mouse. However, the detailed mechanism of altered exocytosis remains elusive. Here, we investigated single synaptic vesicle dynamics in our HD knock-in mouse model (zQ175). In order to observe the single synaptic vesicles, we used synaptotagmin1-antibody conjugated quantum dot to label single synaptic vesicles in presynaptic terminals of cortical neurons of zQ175. Using dual-focus optics and quenching by trypan blue, we are able to track single synaptic vesicles in three dimensions with a 10Hz imaging frequency up to the moment of exocytosis. We observed altered net displacement of released synaptic vesicles in HD cortical neurons, compared with WT. Consistently, radius of gyration of HD before exocytosis released synaptic vesicles were significantly different from WT cortical neurons. These results indicate that the mobility of synaptic vesicles in HD neurons is altered before they reach their fusion site. We also observed much more abnormal movement of non-releasing synaptic vesicles in HD neurons compared with WT neurons. Moreover, the radius of gyration and instantaneous speed of HD non-releasing synaptic vesicles were significantly different from WT neurons. Thus, we conclude that synaptic vesicles dynamics is altered in cortical neurons at the early stage of HD.

Disclosures: **S. Chen:** None. **X. Qin:** None. **H. Park:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.14/F4

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Targeted protein degradation of mutant Huntingtin aggregates: *In vitro* assays and tools to support development of mHTT targeting PROTACs

Authors: F. HERRMANN[1], B. BALDO[1], J. P. SCHUELKE[2], S. MUELLER[2], S. BLENCKE[2], M. HOTZE[1], K. WRONKA-SCHMIDT[1], K. SCHAEFER[1], P. JOHNSON[3], M. PRIME[3], R. FILIPPO[3], J. VILE[3], A. JARVIS[3], ***E. VAN DER KAM**[1], V. KHETARPAL[4], I. MUNOZ-SANJUAN[4], C. DOMINQUEZ[4], M. LEE[4], L. LIU[4], J. A. BARD[5];
[1]Evotec SE, Hamburg, Germany; [2]Evotec, Munich, Germany; [3]Evotec Ltd, Abingdon, United Kingdom; [4]CHDI Management, Inc., Los Angeles, CA; [5]CHDI Management, Inc., Princeton, NJ

Abstract: Since Huntington's disease (HD) is caused by expression of mutant huntingtin (mHTT) protein, lowering expression of mHTT is a key therapeutic strategy for HD. Reducing the amount of mHTT protein in HD-affected brains is predicted to prevent cellular dysfunction, neurodegeneration and alleviate symptoms of the disease. To date, HTT-lowering approaches include antisense oligonucleotides and RNA interference targeting mRNA, zinc finger transcriptional repressors, and CRISPR-Cas9 methods by targeting DNA. Alternative modalities to enhance protein clearance pathways e.g. the autophagy-lysosome pathway and the ubiquitin-proteasome system (UPS) are under investigation. PROteolysis TArgeting Chimera (PROTAC)-based approaches utilize heterobifunctional molecules to simultaneously bind both the target and an ubiquitin E3 ligase to promote the ubiquitination and degradation of the target molecule. Previously, we have described the development of mHTT aggregate binding molecules for PET imaging in animal models of HD and HD patients. We are now interested in exploring the therapeutic potential of small molecules to reduce accumulation of mHTT aggregates by utilizing them as the target-directed warheads for PROTAC-induced proteasomal degradation. Here, we present tools and assays established to support development of such mHTT-targeting PROTACs. We generated a comprehensive chemistry toolbox of mHTT-PROTACs containing a variety of mHTT "warheads" and E3 ligase recruiters conjugated via different PEG linker lengths. For efficient PROTAC-mediated protein degradation, several complex processes need to occur. Therefore, we have developed *in vitro* assays to investigate target binding, E3-ligase recruitment and HTT lowering. Additional assays to investigate ternary complex formation and target ubiquitination are in development. Finally, we present first proof-of-concept experiments indicating successful reduction of transiently-expressed mHTT protein in HeLa cells. Future work will focus on confirmation of the Mechanism of Action (MoA) via the UPS and testing of HTT PROTACs in neuronal cell lines.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.15/F5

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: EPSRC Project 513279 Task D-MAT Award 159190

Title: Development of translational imaging biomarkers of disease progression in a mouse model of Huntington's disease

Authors: *L. RIGGALL[1,2,3,4], E. DEMETRIOU[3], B. SIOW[4], G. P. BATES[1], X. GOLAY[3]; [1]HD Centre, Dept. of Neurodegenerative Dis. & UK Dementia Res. Inst., [2]Dept. of Med. Physics & Biomed. Engin., [3]Dept. of Brain Repair & Rehabil., Univ. Col. London, London, United Kingdom; [4]MRI Unit, Francis Crick Inst., London, United Kingdom

Abstract: Huntington’s disease (HD) is a genetic neurodegenerative disorder due to an abnormally expanded CAG triplet repeat region in the *HTT* gene. Magnetic resonance imaging (MRI) has been used to better understand the pathogenesis and progression of HD, but has so far focused on anatomical rather than metabolic changes. However, these may provide earlier and more sensitive biomarkers. Therefore, this project aims to reveal the metabolic processes occurring throughout HD by using *in vivo* MRI approaches in the R6/2 mouse model. R6/2 mice express exon 1 of the *HTT* gene containing ~180 CAGs, and develop HD-like symptoms including cognitive and motor deficits. To begin undertaking a time-course analysis of metabolites, chemical exchange saturation transfer (CEST), was used in R6/2 and wild type (WT) littermate controls at late-stage (12-weeks-old, n = 10 in both groups). CEST is a contrast enhancement technique that enables the indirect detection of metabolites with exchangeable protons. Post-imaging, cellular and molecular techniques were also utilised to validate MRI measures. Two different CEST irradiation amplitudes were used to target protons exchanging at different rates. MTR asymmetry was then used to investigate changes in metabolites important in HD in R6/2 mice, based on the acquisition giving the greatest level of contrast. Preliminary investigations suggest there is a significant reduction in both amide proton hydrolysis and transfer in late-stage R6/2 mice compared to WT controls, indicating changes in mobile proteins and peptides or pH. A significant increase in magnetisation transfer signal was also observed in R6/2 mice, suggesting further alterations in restricted proton species. CEST may, therefore, have

the potential to reveal changes in metabolic processes that contribute to or are altered in HD pathology over time, and provide non-invasive and sensitive biomarkers of pathogenesis. Assessments will now be extended to earlier disease stages, to enable a time-course characterisation of HD for the identification of robust, translational imaging biomarkers by which to track progression and inform therapeutic intervention.

Disclosures: L. Riggall: None. **E. Demetriou:** None. **B. Siow:** None. **G.P. Bates:** None. **X. Golay:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.16/F6

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI JSC Grant

Title: Investigating the role of SRSF6 in incomplete splicing of Htt mRNA in Huntington's disease mice

Authors: *M. A. MASON[1], C. GOMEZ PAREDES[1], A. NEUEDER[2], A. S. PAPADOPOULOU[1], G. P. BATES[1];
[1]UCL Queen Square Inst. of Neurol., London, United Kingdom; [2]Dept. of Neurol., Ulm Univ., 89081 Ulm, Germany

Abstract: Huntington's Disease (HD) is a monogenic neurodegenerative disease caused by an expanded CAG repeat in exon 1 of Huntingtin (*HTT*). The disease is marked by motor, cognitive and psychiatric symptoms than may manifest in childhood or adulthood. Incomplete splicing of *HTT* has recently emerged as a pathogenic mechanism in HD. The *HTT* gene has 67 exons, and with an expanded CAG repeat length *HTT* does not always splice from exon 1 to exon 2, resulting in an transcript that terminates at a cryptic polyadenylation site in intron 1. This mature *HTTexon1* mRNA encodes the N-terminal HTT exon 1 protein that is known to be highly pathogenic in many model systems. Serine/arginine-rich splicing factor 6 (SRSF6) was predicted to bind to CAG repeats and was previously found to reduce levels of incomplete splicing of a mouse *Htt* minigene in cell culture. To investigate whether SRSF6 plays a role in incomplete splicing *in vivo*, we crossed *Srsf6* knock out (KO) mice to zQ175 neo-deleted knock-in (zQ175DN KI) HD mice. We used a QuantiGene expression assay to analyse 2-month old brain and peripheral tissues. As homozygous *Srsf6* KO is embryonic lethal in mice, we were limited to using *Srsf6* heterozygous mice only. However, heterozygosity for *Srsf6* KO did not change levels of incomplete splicing in zQ175DN KI mice. Next, we sought to generate a cell model of incomplete *Htt* splicing in which *Srsf6* could be knocked down further using siRNAs. zQ175DN

KI mouse embryonic fibroblasts (MEFs) were generated due to their high levels of incomplete splicing. Despite ablation of SRSF6 protein in MEFs 3 and 4 days after treatment with *Srsf6*-targeted siRNAs, levels of incomplete splicing remained unchanged compared to vehicle treated MEFs. Therefore, SRSF6 may not play a role in incomplete *Htt* splicing *in vivo* or cell culture. Further work is needed to fully understand the mechanisms of incomplete *HTT* splicing. Using recently published proteomics data, we have identified other possible modifiers of incomplete splicing (e.g. hnRNP C1/C2). Our zQ175DN KI MEFs can be used to investigate whether these proteins play a role in incomplete splicing of *Htt.* Identification of modifiers could inform the design of *HTT* RNA-targeting therapeutics that may reduce levels of the toxic exon 1 HTT protein isoform generated by incomplete splicing.

Disclosures: M.A. Mason: None. **C. Gomez Paredes:** None. **A. Neueder:** None. **A.S. Papadopoulou:** None. **G.P. Bates:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.17/F7

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: CHDI JSC GRANT

Title: Investigating the mechanisms of heat shock response impairment in Huntington's disease

Authors: *C. GOMEZ-PAREDES, M. A. MASON, A. S. PAPADOPOULOU, G. P. BATES; Huntington’s Dis. Centre, Dept. of Neurodegenerative Disease, UCL Inst. of Neurolog, Univ. Col. London, London, United Kingdom

Abstract: Huntington’s disease (HD) is a neurodegenerative disorder caused by an abnormal CAG expansion within exon 1 of the huntingtin (*HTT)* gene, which leads to the formation of aberrantly-folded HTT proteins that are highly prone to aggregation. The heat shock response (HSR) is a mechanism responsible for the maintenance of proteome integrity within cells. HSR is induced when cells are exposed to proteotoxic stress such as the presence of HTT aggregates as is observed in HD. The master regulator of the HSR is HSF1, which regulates the transcriptional activation of the heat shock genes. A key step during the attenuation of the HSR is the acetylation of a lysine residue in HSF1. The deacetylation of this residue can be mediated by the histone deacetylase SIRT1. The pharmacological activation of the HSR is a promising therapeutic strategy in HD. Previously, our group reported that pharmacological induction of the HSR led to a reduction in the levels of aggregation in HD mouse models. However, the effects were transient as the ability to induce a HSR became impaired with the disease progression (Labbadia *et al.,* 2011). Our aim is to study the mechanisms involved in the progressive

impairment of the HSR in HD and if this could be ameliorated with *Sirt1* overexpression. We employed NVP-HSP990 (an HSP90 inhibitor that releases HSF1 from its HSP90 inhibitory complex) to induce HSR in HD mice (R6/2) overexpressing *Sirt1* (*n*=6/treatment group) at 9 weeks of age. Brain and muscle tissues were collected at several timepoints after dosing. A QuantiGene multiplex gene expression assay was established to measure the expression of 9 heat shock genes and their regulators. Preliminary data indicated that there was a trend towards improvement in HSR induction for some heat shock genes in R6/2 mice overexpressing *Sirt1* compared to R6/2 after NVP-HSP990 treatment. However, this difference did not reach statistical significance at these timepoints. *Sirt1* overexpression may have an effect on the kinetics of induction of the HSR in HD mice after dosing with NVP-HSP990. This requires further investigation at additional timepoints post dosing.

Disclosures: C. Gomez-paredes: None. **M.A. Mason:** None. **A.S. Papadopoulou:** None. **G.P. Bates:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.18/F8

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Huntingtin promotes cadmium neurotoxicity and neurodegeneration in striatal cells via altered metal transport, mitochondrial dysfunction, and protein kinase C delta dependent oxidative stress and apoptosis signaling mechanisms

Authors: *G. KWAKYE[1], M. THOMAS[1], W. CHEN[1], J. JIMENEZ[1], M. SAITO[2], M. MCILVIN[2];
[1]Neurosci., Oberlin Col., Oberlin, OH; [2]Marine Chem. and Geochemistry, Woods Hole Oceanographic Inst., Woods Hole, MA

Abstract: Huntington’s disease (HD) is functionally linked to environmental factors including cigarette use and dyshomeostasis in the levels of metals. Interestingly, one of the most abundant heavy metals in cigarettes is cadmium (Cd), which also accumulates in the striatum and causes neurotoxicity upon exposure. Thus, we hypothesized that heterozygous huntingtin (HTT), responsible for the majority of cases of HD in patients, in combination with Cd exposure would cause neurotoxicity and neurodegeneration via increased intracellular accumulation of Cd and activation of oxidative stress signaling mechanisms in a mouse striatal cell line model of HD. We report that heterozygous HTT striatal cells are significantly more susceptible to Cd-induced cytotoxicity as compared to wild-type HTT cells upon exposure for 48 h. The heterozygous HTT and Cd-induced cytotoxicity led to a NADPH oxidase (NOX) mediated oxidative stress that was attenuated by exogenous antioxidants and a NOX inhibitor, apocynin. Heterozygous HTT

coupled with Cd exposure caused increased expression of protein kinase C δ (PKCδ) and other key oxidative stress proteins levels, enhanced the activation of caspase-9 and caspase-3 mediated apoptosis, and blocked the overexpression of extracellular signal-regulated kinase (ERK). We observed significantly greater intracellular accumulation of Cd and reduced expression of divalent metal transporter 1 (DMT1) protein in the heterozygous HTT striatal cells upon Cd exposure. Treatment with zinc, manganese, and iron as well as exogenous antioxidants significantly attenuated the Cd-induced cytotoxicity. Collectively, these results demonstrate that heterozygous HTT exhibits greater neurotoxic properties when coupled with Cd exposure to cause cell death via caspase mediated apoptosis, altered metal transport, and modulation of ERK and PKCδ dependent oxidative signaling mechanisms.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.19/F9

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Phosphoproteomic analysis of TrkB receptor activation with a novel monoclonal antibody agonist: Implications for the treatment of Huntington's disease

Authors: B. KRACHER[1], J. P. SCHUELKE[1], N. CARTY[2], B. HUSCHER[2], A. GAERTNER[2], G. BURSOVA[2], T. SCHWAGARUS[2], L. MICHOLT[2], *H. VON DER KAMMER[2], **E. VAN DER KAM**[2], J. A. BARD[3], J. ROSINSKI[3], I. MUNOZ-SANJUAN[4], V. BEAUMONT[4]; [1]Evotec, Munich, Germany; [2]Evotec SE, Hamburg, Germany; [3]CHDI Management, Inc., Princeton, NJ; [4]CHDI Management, Inc., Los Angeles, CA

Abstract: Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by CAG expansions in the huntingtin gene (*HTT*). Alterations in the neurotrophin tyrosine receptor kinase (TrkB) signaling pathways is thought to contribute to HD pathophysiology. Brain-derived neurotrophic factor (BDNF)-mediated activation of TrkB is a key pathway for neuronal survival, differentiation and synaptic plasticity. A reduction of BDNF in the striatum, cortex and hippocampus from HD post-mortem brain tissue and reduced cortico-striatal BDNF trafficking in HD mouse models has been described, whilst other reports have demonstrated normal levels of BDNF but impaired downstream TrkB receptor signaling. Our current study investigates a potential therapeutic approach to reverse deficits in HD through activation of BDNF - TrkB signaling in HD mouse models using a novel mouse TrkB agonistic monoclonal antibody, 38B8. We injected the antibody intrastriatally and investigated the proximal effects on the proteome and phosphoproteome in wild type and zQ175DN

heterozygous mice at 2 months (presymptomatic) and 9 months of age (symptomatic). While the global protein levels are largely unaffected 4 hours after antibody application, we found close to 300 significantly affected phosphorylation sites, most of which showed increased phosphorylation. Several of these sites are on proteins involved in neutrophin signaling and our analyses provide evidence for an activation of all three major branches of the pathway. Overall, the observed treatment response was similar in both young and aged wild type and zQ175DN heterozygous mice and we did not detect any significant differences between the genotypes. Functional enrichment analyses revealed that proteins with regulated phosphorylation sites are mostly involved in regulation of gene expression, more specifically in mRNA transport, ribosome biogenesis and translation initiation. This outcome matches known consequences of early activated neutrophin signaling and supports data that 38B8 acts as specific TrkB agonist, which can induce equivalent responses in both wild type and mutant genetic background. Our findings demonstrate the functional activity of 38B8 *in vivo*, which supports that direct TrkB receptor activation is a viable approach for the treatment for HD.

Disclosures: **B. Kracher:** None. **J.P. Schuelke:** None. **N. Carty:** None. **B. Huscher:** None. **A. Gaertner:** None. **G. Bursova:** None. **T. Schwagarus:** None. **L. Micholt:** None. **H. Von Der Kammer:** None. **E. van der Kam:** None. **J.A. Bard:** None. **J. Rosinski:** None. **I. Munoz-Sanjuan:** None. **V. Beaumont:** None.

Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

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Program #/Poster #: 474.20/F10

Topic: C.04. Movement Disorders other than Parkinson's Disease

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Jean Perkins Foundation

Title: Structural neuroimaging and biofluid markers of treatment response in Huntington’s disease: Preclinical evidence with the $p75^{NTR}$ ligand, LM11A-31

Authors: *D. A. SIMMONS[1], B. D. MILLS[2], J. KUAN[1], J. ZHOU[1], T. L. MCHUGH[1], C. AKERS[2], W. SYRIANI[1], M. ZEINEH[2], F. M. LONGO[1];
[1]Neurol. and Neurolog. Sci., [2]Radiology, Stanford Univ., Stanford, CA

Abstract: Huntington’s disease (HD) is caused by an expansion of the CAG repeat in the huntingtin gene and is characterized predominately by striatal neurodegeneration. HD therapeutic development would be facilitated by translatable biomarkers of treatment response.

In HD patient and mouse studies, volumetric magnetic resonance imaging (MRI) and plasma cytokines have been suggested as biomarkers of disease onset/progression but their ability to detect treatment efficacy is understudied. We designed a cross-sectional study of male and female R6/2 mice to assess if structural neuroimaging and meso scale discovery-based biofluid assays can detect treatment effects using the $p75^{NTR}$ ligand LM11A-31 (C31). We previously showed that C31 reduced the HD phenotype in mouse models of the disease. C31 is in a phase 2a clinical trial for Alzheimer's disease, thus translatable biomarkers able to detect its therapeutic effects would expedite its advancement to HD clinical testing. C31 or vehicle (veh) was orally administered (50 mg/kg, once daily 5 days/week) to 4-5 week old R6/2 and wild-type (WT) mice for 7 weeks. At 11-12 weeks of age, MRI, diffusion tensor imaging (DTI) and R2* relaxometry was performed and biofluid samples were collected. T2-weighted MRI revealed significant atrophy in multiple brain regions including striatum of R6/2-veh mice versus wild-types (WTs) which was alleviated with C31 treatment. *In vivo* MRI volumes correlated strongly with those measured *ex vivo* via stereology on Nissl-stained sections. DTI was used to measure mean diffusivity, fractional anisotropy, and neurite orientation dispersion index. The striatum of R6/2-veh mice showed changes in DTI metrics that were consistent with those seen in HD patients and suggest disrupted microstructure, connectivity, and iron levels. C31 partially prevented these changes. C31 also diminished increases in plasma cytokine levels in R6/2 mice including TNFα and IL-6. Finally, we measured urinary levels of the extracellular domain (ecd) of $p75^{NTR}$, a cleavage product released with pro-apoptotic ligand binding that detects progression of other neurodegenerative diseases. Urinary $p75^{NTR}$-ecd was increased in by 44% in R6/2-veh mice and negatively correlated with regional volumes; C31 reduced this increase. These results are the first to show that urinary $p75^{NTR}$-ecd levels are elevated in an HD mouse model and that they can detect therapeutic effects. These findings also suggest that structural MRI and plasma cytokine levels can detect treatment response and that using combinations of these biomarkers would be a viable and powerful option for clinical trials.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.21/F11

Topic: C.04. Movement Disorders other than Parkinson's Disease

Title: Huntington's disease screening platforms for mRNA HTT quantification: ViewRNA vs TaqMan qPCR

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Abstract: Over the last years there has been a heave of new therapeutic modalities which are no longer limited to target proteins but also DNA and RNA. These include antisense oligonucleotides (ASO), genome editing such as CRISPR or Zing fingers and small molecules targeting RNA such as splicing modulators or RIBOTACs. With this shift in targets has come the need of developing new techniques or adapting existing ones to formats that would allow for high-throughput screen of therapeutic compounds.
Lowering of the pathogenic mutant huntingtin (mHTT) protein in Huntington's disease (HD) is one of the leading therapeutic approaches to ameliorate the fatal neurodegeneration caused by the poly-CAG expansion in the HTT gene. Recent promising results in Phase 1/2 clinical trials with ASO therapy in HD patients, in addition to animal model data linking a reduction in mutant huntingtin levels to improved symptoms, mHTT mRNA is increasingly being considered an important therapeutic target in HD.
Despite positive ASO clinical trial results, there is still a need to identify small molecules to overcome the challenges of invasive administration, selectivity and poor distributions. Identifying brain-penetrant small molecules with suitable oral dosing would potentially be advantageous over novel biological agents. As such there is a need to develop a robust and high-throughput screening assay that will quantifiably measure levels of HTT mRNA.
CHDI with Charles River Early Discovery are currently using two different techniques, ViewRNA and TaqMan qPCR assays for RNA compound and siRNA screens. In this poster we will present the use of these techniques in evaluating small molecules for the treatment of HD. We will present our initial ViewRNA assay development, compare the technology to the more established TaqMan qPCR assay and evaluate its potential for utilization in a HTS campaign to identify HTT mRNA modulators.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.22/F12

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Field Neurosciences Institute
CMU Neuroscience Program
College of Medicine
John G. Kulhavi Professorship in Neuroscience at CMU

Title: Comparison of ovine and bovine sources of GM1 ganglioside as a treatment for Huntington's disease in YAC128 mice model

Authors: *S. KONERU[1,2], B. KATHIRVELU[1,3,4], B. MACDONALD[1,2], D. ELDRED[1,2], M. RESK[1,2], N. FETTINGER[1,2], M. I. SANDSTROM[2,5], U. HOCHGESCHWENDER[2,4], P. MAITI[2,6], J. ROSSIGNOL[1,2,4], G. L. DUNBAR[1,2,5,6];
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Abstract: Huntington's disease (HD) is a neurodegenerative genetic disorder caused by mutations in the HTT gene containing an abnormally long polyglutamine (CAG) stretch. This leads to excessive production and accumulation of mutant huntingtin protein (mHTT) in the brain. The excessive mHTT protein accumulation causes progressive motor, psychiatric, and cognitive decline and eventually leads to neuronal death. Given that only palliative treatments are available and no effective treatment has been approved, researchers are looking at a variety of potential therapeutics for HD, including the use of GM1 ganglioside. GM1 ganglioside is a sialic acid-containing glycosphingolipid that is found abundantly in the outer leaflet of the neuronal membrane in the brain. GM1 gangliosides play a vital role in cell signaling, calcium homeostasis and cell-cell interactions in the brain. In HD patients, GM1 ganglioside levels are decreased, which contribute to HD symptomology and disease progression. Previous studies found that treatment with GM1 ganglioside obtained from bovine sources improves motor dysfunction in HD rodent models. However, GM1 gangliosides that are obtained from ovine sources are more economical than bovine sources and the goal of our experiment was to test whether the ovine source can produce similar effects in improving motor and cognitive dysfunctions in HD. In our current study, we used intraventricular osmotic pumps to deliver GM1 gangliosides that are obtained from ovine and bovine sources for six weeks in eight to nine months YAC128 mouse model. We used rotarod-, open field-, catwalk-, Barnes maze-, novel-object-recognition- and elevated-plus- maze- tasks to measure motor and non-motor parameters. Our preliminary results indicate that both bovine and ovine sources of GM1 tended to reduce behavioral deficits in YAC128 mice on the rotarod-, open fields-, Barnes maze-, but not on novel-object-recognition-, catwalk-, and elevated-plus-maze- tasks.

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Poster

474. Molecular Mechanisms of Huntington's Disease

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 474.23/F13

Topic: C.04. Movement Disorders other than Parkinson's Disease

Support: Agence Nationale de la Recherche (ERA-NET Neuron8 “SMART”)
France Parkinson Foundation

Title: Retinoic acid receptor beta protects striatopallidal medium spiny neurons from mitochondrial dysfunction and neurodegeneration

Authors: *W. KREZEL[1], M. CIANCIA[1], M. RATAJ[1], A. NIEWIADOMSKA-CIMICKA[1], V.-A. BALDASSARRO[1], A.-L. CHARLES[2], B. GENY[2];
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Abstract: Transcriptional dysregulation observed in Huntington’s disease (HD) may underlay different aspects of HD physiopathology, but the exact mechanisms of the cause and effect of such dysregulation is not clear. Here we show that retinoic acid receptor beta (RARb), a transcription factor strongly downregulated in the striatum of HD patients and mouse models of HD displays neuroprotective activity of striatopallidal medium spiny neurons (MSNs) in mouse. In line with such function, abolished RARb signalling in *Rarβ*$^{-/-}$ mice leads to postnatal loss of a subpopulation of striatopallidal MSNs expressing dopamine D2 receptor (D2R) and behavioural abnormalities including deficits in motor coordination. Our data indicate that this increased sensitivity of D2R^{+} MSNs to cell death may result from abnormal mitochondrial morphology and functions in *Rarβ*$^{-/-}$ striatum. Accordingly, pharmacological increase of calcium concentration using suboptimal doses of thapsigargin, leads to rapid mitochondrial fragmentation and cell death in cultured *Rarβ*$^{-/-}$ MSNs, whereas suboptimal doses of 3-nitropropionic acid, an inhibitor of mitochondrial complex II/ succinate dehydrogenase leads to the loss of D2R^{+} striatopallidal MSNs in *Rarβ*$^{-/-}$, but not in WT mice *in vivo*. Our data point to relevance of compromised RARb signalling in increased sensitivity and loss of D2R^{+} MSNs in HD and point to RARb as a new potential therapeutic target in this disease.

Disclosures: **W. Krezel:** None. **M. Ciancia:** None. **M. Rataj:** None. **A. Niewiadomska-Cimicka:** None. **V. Baldassarro:** None. **A. Charles:** None. **B. Geny:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.01/F14

Topic: C.06. Neuromuscular Diseases

Support: United States Department of Veterans Affairs (IK2RX002688)

Title: Dental pulp stem cell secretome therapy in a mouse model of amyotrophic lateral sclerosis

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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating motor neuron (MN) disease with no cure. Mounting evidence indicates that ALS is a complex disease involving interaction between central glia and the peripheral immune response and neuromuscular interface. Stem cell secretomes contain various trophic factors and cytokines that are beneficial in a variety of conditions. We recently demonstrated that administration of the secretome in adipose-derived stem cell conditioned medium (ASC-CM) during early neuromuscular junction (NMJ) denervation ameliorated NMJ disruption in the mutant superoxide dismutase ($mSOD1^{G93A}$) ALS mouse model. In the present study, we investigated whether dental pulp stem cell conditioned medium (DPSC-CM) therapy at different stages of disease could promote NMJ preservation, prevent MN loss and extend lifespan. We found that DPSC-CM significantly reduced NMJ denervation at postnatal day (PD)47 compared to vehicle-treated $mSOD1^{G93A}$ mice ($P<0.05$). When administered during late pre-symptomatic stages (PD70-P91), DPSC-CM significantly increased MN survival ($P<0.01$) and NMJ preservation ($P<0.05$). For $mSOD1^{G93A}$ mice treated with DPSC-CM beginning at symptom onset through end-stage, days of survival post-onset, as well as overall lifespan, was significantly increased compared to vehicle-treated mice. This study is the first to show the therapeutic benefits of systemic DPSC secretome in an animal model of ALS. Importantly, this is the first report of stem cell secretome effects at multiple stages of ALS disease progression. Our study establishes a foundation for future research related to the treatment effects of DPSC and other stem cell secretome therapies in ALS.

Disclosures: J. Wang: None. **K. Zuzzio:** None. **C. Walker:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.02/F15

Topic: C.06. Neuromuscular Diseases

Support: Regione Lombardia TRANS-ALS Project

Title: Morpholino oligomers ameliorate pathological phenotype in C9orf72 ALS iPSC-derived lines

Authors: *G. P. COMI[1], **M. TAIANA**[1], M. BERSANI[1], F. BIELLA[1], M. NIZZARDO[1], C. KIZILIRMAK[2], P. RINCHETTI[1], S. BARABINO[2], N. BRESOLIN[1], S. CORTI[1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal disorder characterized by progressive degeneration of motor neurons (MNs). GGGGCC repeat expansions in C9ORF72 gene are the most common identified genetic cause, and even if their pathogenic processes are still unknown, many possible mechanisms have been proposed, including loss of function of the C9Orf72 protein and gain of function caused by accumulation of RNA expansion foci that can sequestrate RNA binding proteins (RBPs), and by dipeptide repeats proteins (DPRs) produced by repeat-associated non-ATG (RAN) translation. Patient-specific induced pluripotent stem cells (iPSC)-derived lines and iPSC-derived MNs are promising and reliable methods to better understand C9-ALS pathogenesis. Therapeutic approaches include the use of antisense oligonucleotides (ASOs) designed to bind complementary mRNA and interfere with specific biological processes. We designed two different ASOs with Morpholino (MO) chemistry: against the C9ORF72 expansion and against the C9ORF72 gene promoter. Using these tools, we aimed to characterize the pathological phenotype of the C9-ALS iPSC-derived lines and evaluate the therapeutic effect of MOs administration on specific pathological markers. We reprogrammed iPSCs from C9-ALS patients and controls and differentiated them into MNs. We investigated the phenotype of the C9-ALS lines compared to controls, evaluating cells survival, RAN products expression, RNA foci presence, dysregulation of putative RBPs interacting with RNA foci, R-loops formation, DNA damage, and Stathmin2 expression. Then, we transfected ALS-MNs with MOs and evaluated any modification of the pathological markers previously identified. We observed that MO-based therapy can rescue pathological features in C9-ALS iPSC-derived lines such as accumulation and mislocalization of the protein involved in nuclear trafficking RanGAP, the RNA binding protein Pur-α, TDP-43 as well as R-loops increase, DNA damage and Stathmin2 decrease. Our results suggest that patient specific iPSCs and iPSC-derived MNs are a valuable

tool to deepen the knowledge of C9ORF72 pathogenic mechanisms, and that MO-mediated approaches represent a promising therapeutic strategy that needs to be further validated.

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Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.03/F16

Topic: C.06. Neuromuscular Diseases

Support: Target ALS Grant

Title: Development of neuronal cell line assays to assess the effects of small molecules on ALS-associated TDP-43 pathologies and toxicity

Authors: *H. J. WOBST[1], M. AIKIO[2], D. G. BROWN[4], N. J. BRANDON[1], S. J. MOSS[3]; [1]Discovery Biology, Neuroscience, R&D BioPharmaceuticals, AstraZeneca, Boston, MA; [2]AstraZeneca-Tufts Lab. for Basic and Translational Neurosci., [3]Dept. of Neurosci., Tufts Univ., Boston, MA; [4]Hit Discovery, Discovery Sciences, R&D BioPharmaceuticals, Astrazeneca, Boston, MA

Abstract: Mutations in the RNA-binding and -processing protein TDP-43 cause rare familial forms of amyotrophic lateral sclerosis (ALS). Moreover, in the majority of ALS cases (~97%) as well as almost half the cases of frontotemporal dementia (FTD) post mortem analysis reveals TDP-43 pathologies in affected tissues. These pathologies include cytoplasmic mislocalization, formation of TDP-43 inclusions and aberrant phosphorylation. Using the neuronal cell lines NSC-34 and SH-SY5Y we can reproduce TDP-43 proteinopathy-associated phenotypes including TDP-43 toxicity, TDP-43 aggregation and hyperphosphorylation at the disease-associated S409/410 site. We identified several series of compounds which were active in a TPD-43 toxicity model in *C. elegans*. We tested representative actives in NSC-34 cells overexpressing TDP-43 to confirm activity in mammalian cells. Furthermore, we investigated whether compounds that rescue toxicity in *C. elegans* and mammalian cells affect TDP-43 aggregation and hyperphosphorylation. Broadly, we identified two classes of compounds: 1.) compounds that rescue TDP-43 toxicity as well as TDP-43 pathologies such as aggregation and/or phosphorylation in mammalian cells; 2.) compounds that rescue TDP-43 toxicity, but not TDP-43 aggregation and/or phosphorylation. Specifically, we found that a series of MAP kinase p38α inhibitors rescue TDP-43 overexpression-induced toxicity in *C. elegans* and mammalian cells. Both genetic and chemical inhibition of p38α reduced S409/410 TDP-43 phosphorylation

and delayed aggregation. In summary, we developed a set of mammalian cell assays to confirm actives from a *C. elegans* screen and investigate whether modulation of ALS-associated TDP-43 pathologies is linked to the rescue of TDP-43 toxicity.

Disclosures: H.J. Wobst: A. Employment/Salary (full or part-time):; AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca. **M. Aikio:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. **D.G. Brown:** A. Employment/Salary (full or part-time):; AstraZeneca. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca. **N.J. Brandon:** A. Employment/Salary (full or part-time):; AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca. **S.J. Moss:** A. Employment/Salary (full or part-time):; Tufts. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); AstraZeneca. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca. F. Consulting Fees (e.g., advisory boards); AstraZeneca.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.04/F17

Topic: C.06. Neuromuscular Diseases

Support: Target ALS Industry Led Consortia Grant

Title: Deconvolution of a high throughput phenotypic screen in yeast identifies modulators of C9orf72 toxicity

Authors: *D. G. BROWN[1], H. J. WOBST[2], C. BARDELLE[3], D. MURRAY[3], I. FEIERBERG[1], L. LEACH[3], K. MACK[4], R. CUPO[4], E. BARBIERI[4], A. D. GITLER[5], N. KRAMER[5], J. SHORTER[4], K. ABIRAMAN[6], S. MOSS[6], N. J. BRANDON[2];
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Abstract: Repeat G4C2 expansions in the C9orf72 gene leading to poly-PR proteins has been linked to approximately 11% of known cases of ALS. A yeast strain expressing the C9orf72 dipeptide repeat proteins (PR_{50}) was constructed in a drug-pump deletion background. This strain showed a toxic phenotype which was subsequently used to identify compounds that could rescue this toxicity. The strain was screened against a set of 500K diverse compounds using a high-content flow cytometry assay. Several series of compounds were discovered which rescued the toxic phenotype in yeast and then confirmed in the same strains using an optical density read-out. A target analysis was conducted using the target annotation from the screening library, and then matched against those targets which possessed both yeast and human orthologs. Roughly 50% of the hits were not associated with known targets and work was undertaken to identify these unknown targets in yeast. Multiple photoaffinity probes were synthesized across five chemical series to identify new targets through mass spectrometry-based chemo-proteomics. We will discuss the overall strategies and methods used as well as progress made towards target validation.

Disclosures: **D.G. Brown:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals. **H.J. Wobst:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals. **C. Bardelle:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals. **D. Murray:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals. **I. Feierberg:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals. **L. Leach:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals. **K. Mack:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **R. Cupo:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **E. Barbieri:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **A.D. Gitler:** A. Employment/Salary (full or part-time):; Stanford University. **N. Kramer:** A. Employment/Salary (full or part-time):; Stanford University. **J. Shorter:** A. Employment/Salary (full or part-time):; University of Pennsylvania. **K. Abiraman:** A. Employment/Salary (full or part-time):; Tufts University. **S. Moss:** A. Employment/Salary (full or part-time):; Tufts University. **N.J. Brandon:** A. Employment/Salary (full or part-time):; AstraZeneca Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); AstraZeneca Pharmaceuticals.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.05/F18

Topic: C.06. Neuromuscular Diseases

Title: ATXN2, a modifier of TDP43 pathology is a new therapeutic target for amyotrophic lateral sclerosis

Authors: *Y. HU[1], Y. WANG[1], U.-M. LIM[4], A. FERNANDIS[4], J. EICHER[2], D. STONE[3], S. PARMENTIER-BATTEUR[1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease caused by the loss of lower and upper motor neurons leading to progressive muscle weakness and respiratory failure. Although multiple gene mutations can cause ALS, protein and RNA aggregates are major hallmarks of ALS pathology. Ninety-seven percent of ALS patients present TDP43 pathology including aberrant cytoplasmic mislocalization and aggregation with hyper-phosphorylation, C-terminal cleavage and ubiquitination. Phenotypic-based approach has identified Ataxin-2 (ATXN2) as a potent modifier of TDP43-toxicity and this original finding has been confirmed in more relevant *in vivo* models. The goals of our research are 1) to validate the role of ATXN2 in ALS hu-iPSC-neuronal models and 2) to identify the best strategy to modulate ATXN2 activity. Our results showed that knockdown of ATXN2 using lenti-shRNA can significantly attenuate the accelerated neuronal cell death and TDP43-mislocalization in hu-iPSC neurons-derived from ALS patients with C9ORF72 expansion and in AAV8-syn1 mediated TDP43 overexpressing hu-iPSC neurons. Knockdown of ATXN2 also reduced TDP43-containing stress granule formation in hu-iPSC neurons stressed with Sodium-Arsenite. A proteomic study was used to explore the change of ATXN2 interactome in presence of TD43 overexpression in hu-iPSC neurons and identified major pathways including proteins known to be implicated in nuclear/cytoplasmic transport and stress granules formation. Mutation of TDP43 RRM1 and RRM2 domains reduced the interaction of TDP43 with ATXN2, and abolished TDP43 toxicity similarly to ATXN2 knock-down suggesting that inhibition of TDP43/ATXN2 interaction may be a promising strategy for therapeutic intervention. Development and validation of High Throughput Screening enabling assays are established to identify tool compounds toward the validation of this novel strategy against TDP43-induced pathology.

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Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.06/F19

Topic: C.06. Neuromuscular Diseases

Title: Identification of novel hit compounds using a high-throughput phenotypic screen with SMA patient iPSC-derived motor neurons

Authors: *M. L. HENDRICKSON[1], P. GUYETT[1], J. KOUZNETSOVA[2], W. ZHENG[2], Z.-W. DU[1];
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Abstract: Spinal muscular atrophy (SMA) is an inheritable cause of infant mortality that is characterized by the loss of lower motor neurons and skeletal muscle atrophy. The degeneration of motor neurons is caused by insufficient levels of survival motor neuron (SMN) protein, which is encoded by two nearly identical genes SMN1 and SMN2. Most cases of SMA harbor homozygous deletions of the SMN1 gene and retain at least one copy of SMN2. Hence, a promising treatment strategy is to upregulate levels of the full-length SMN protein originating from the SMN2 gene. Drug discovery screening platforms typically use SMA fibroblasts or lymphocytes, yet the identified molecules often had limited efficacy in SMA mouse models, especially rescuing motor neuron (MN) degeneration. Therefore, MNs from SMA patients should be used early in drug discovery to increase the likelihood of identifying effective small molecule therapeutics. At BrainXell, we established new technologies to rapidly differentiate SMA patient induced pluripotent stem cells (iPSCs) into large quantities of neurons. We also used genome editing to endogenously fuse SMN2 with a nanoluciferase (NLuc) reporter, which enables high-throughput screening (HTS) that monitors the expression levels of SMN after 48 h exposure to each compound. The assay was adapted to meet HTS requirements, including: large batch sizes, 1536-well format, minimal well-to-well variation, short-term culture, plating by automated dispenser, and low reagent volumes. Applying a quantitative HTS approach, we screened the LOPAC, NPC, and MIPE libraries (>6,000 compounds) in a dose dependent manner. After demonstrating feasibility, we expanded the screen to the larger Genesis library (95,000 compounds) in order to identify novel hit molecules. Compounds that increased SMN2 expression by >20% were considered hits. Analysis of the combined 100,000 compound qHTS identified 81 hit candidates, which were rescreened in triplicate. Ten compounds increased SMN2 expression by 20% with EC50 < 10 μM. We then used an ELISA to validate the increased SMN2 expression after 48 h treatment in a non-engineered SMA-patient cell line. This screening paradigm identified and validated 3 new hit compounds that have promising efficacy and potency.

Disclosures: **M.L. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell, Inc. **P. Guyett:** A. Employment/Salary (full or part-time):; BrainXell, Inc.. **J. Kouznetsova:** None. **W. Zheng:** None. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell, Inc..

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.07/DP05/F20

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: C.06. Neuromuscular Diseases

Support: CONACYT a JFR N° 220871
DGAPA-PAPIIT IN214716 JFR

Title: Findings in myotonic distrophy type I by difussion tensor imaging and voxel based morphometry

Authors: ***M. M. LOPEZ-TITLA**[1], L. BELTRAN-PARRAZAL[2], J. FERNANDEZ-RUIZ[3], J. MAGAÑA[4], C. HERNÁNDEZ[1], L. MARQUEZ[5], R. DIAZ[6];
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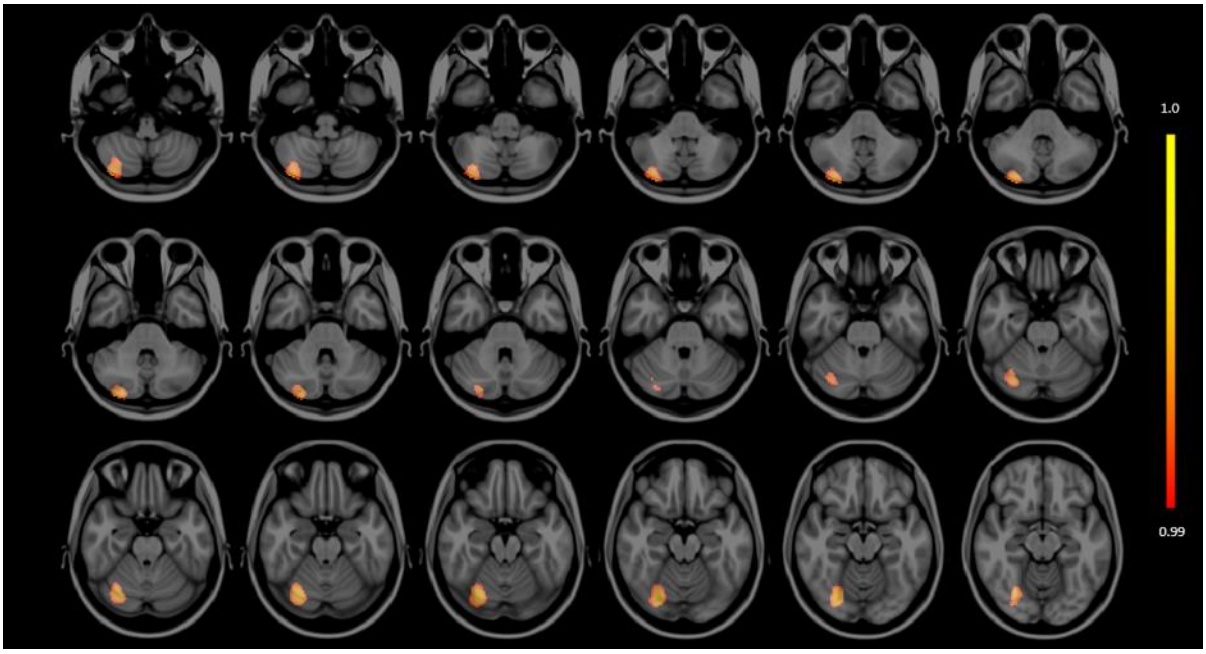
Abstract: Myotonic dystrophy type I (DM1) is a neurodegenerative and hereditary disease. It is due to a genetic mutation on chromosome 19, which is linked to the repetition of the chain of cytosine, thymine and guanine (CTG); the number of these repetitions is less than 50 for healthy subjects. The DM1 symptoms are dependent of the age onset and could vary from patient to patient. DM1 main symptoms are distal muscle weakness and myotonia. This disorder is difficult to diagnose. The objective of this project is to evaluate the integrity of the white matter by Diffusion Tensor Imaging (DTI) and the volume of gray matter by Voxel Based Morphometry (VBM) in patients with DM1. This will help us to find biomarkers useful to characterize the evolution of this disorder resulting in a better diagnosis and prognosis. In the present work 37 DM1 patients and 35 healthy controls volunteer participants were matched by age, sex and level education. They underwent an MRI session in a 3T MR Scanner with a 32 channel Head-Sense Coil. Diffusion tensor images have the following parameters: 33 diffusion directions, b=800s/mm^2, isometric spatial resolution (2mmx2mmx2mm), 70 slices and T1 weighted high resolution images were acquired with a FOV=240x240, 180 sagittal slices and spatial resolution of 1 mm^3 For statistical data analysis un-paired sample t-test was applied for both kind of analysis using FSL 5.0.8 software. DTI images were corrected by movement and eddy currents

and TBSS script was applied. Cluster with statistical significance P<0.01 were found in orbitofrontal white matter regions, anterior cingulate cortex and corpus callosum. Atrophy in white matter paths is significant in frontal brain areas, which imply that different control processes are altered. T1 weighted images were corrected by movement and VBM script was applied clusters with P<0.01 were found in cerebellar and occipital gray matter showing grey matter atrophy in the group of patients. Lobules VI and Crus I cerebellar regions have projections to prefrontal area 46 which is associated with working memory and attention processes.



Disclosures: **M.M. Lopez-Titla:** None. **L. Beltran-Parrazal:** None. **J. Fernandez-Ruiz:** None. **J. Magaña:** None. **C. Hernández:** None. **L. Marquez:** None. **R. Diaz:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.08/F21

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant 1R43NS097080-01A1
DOD CDMRP Grant W81XWH1810556

Title: Amyotrophic lateral sclerosis drug discovery via high-throughput phenotypic screening using induced pluripotent stem cell-derived human motor neurons

Authors: *P. GUYETT[1], M. L. HENDRICKSON[1], J. KOUZNETSOVA[2], Z.-W. DU[1];
[1]BrainXell, Inc., Madison, WI; [2]NCATS, Rockville, MD

Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease primarily affecting motor neurons. Unfortunately, there are only two drugs approved to treat the condition, neither of which increases patient survival by more than a few months. This sobering reality highlights the urgent need for new ALS therapeutic development, which has been plagued by high failure rate during clinical trials. This high failure rate suggests that pre-clinical screening strategies need to be re-evaluated. One of the markers of disease in ALS patients is the aberrantly low expression of neurofilament light chain (NFL) in motor neurons. Further, recovery of NFL to normal levels prevents hallmark phenotypic changes in ALS neurons. Therefore, we wanted to establish a clinically relevant screening platform to identify compounds that return expression of NFL to normal levels in ALS patient derived motor neurons. At BrainXell, we established new technologies to rapidly differentiate ALS patient induced pluripotent stem cells (iPSCs) into large quantities of neurons. We then used genome editing techniques to endogenously fuse NFL with a nanoluciferase (NLuc) reporter, thus enabling a high-throughput screening (HTS) system that monitors the expression levels of NFL after 72 h exposure to each compound. The assay was adapted to meet HTS requirements, including: large batch sizes, 1536-well format, minimal well-to-well variation, short-term culture, plating by automated dispenser, and low reagent volumes. Applying a quantitative HTS approach, we screened the LOPAC, NPC, and MIPE libraries (>6,000 compounds) in a dose dependent manner. Compounds that increase NFL expression by 50% (to approximately normal levels) were considered hits. From these screens we identified 50 hit compounds that are currently going through secondary validation. Preliminary data looks promising. For example, one of these hits restores normal expression of NFL with no observed neurotoxicity. From this work, we established a high-throughput phenotypic screening strategy that is more clinically relevant in order to increase the likelihood of clinical success for any therapeutic candidate that comes out of our drug discovery funnel.

Disclosures: P. Guyett: A. Employment/Salary (full or part-time):; BrainXell, Inc. **M.L. Hendrickson:** A. Employment/Salary (full or part-time):; BrainXell, Inc.. **J. Kouznetsova:** None. **Z. Du:** A. Employment/Salary (full or part-time):; BrainXell, Inc..

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.09/F22

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS100835
ALSA Grant 18-IIA-404

Title: Effect of RAGE pharmacological inhibition in the progression of the disease in hSOD1^{G93A} ALS mouse model

Authors: L. LIU, S. GRAUZAM, K. M. KILLOY, M. R. VARGAS, *M. PEHAR;
Cell and Mol. Pharmacol. and Exptl. Therapeut., Med. Univ. of South Carolina, Charleston, SC

Abstract: Amyotrophic lateral sclerosis (ALS) is characterized by the progressive degeneration of both upper and lower motor neurons. Several lines of evidence indicate that astrocytes play a key role in the progression of the disease. Accordingly, astrocytes isolated from mutant human superoxide dismutase 1 (hSOD1)-overexpressing rodents induce the death of co-cultured motor neurons. We recently identified RAGE, the receptor for advanced glycation end products (AGEs), as a potential effector of astrocyte-mediated neurotoxicity. Motor neuron death induced by hSOD1^{G93A}-overexpressing astrocytes was prevented by RAGE blocking antibodies or two different RAGE pharmacological inhibitors, FPS-ZM1 and RAP. Moreover, motor neurons isolated from RAGE knockout mice were not sensitive to the neurotoxic signal derived from ALS-astrocytes. We previously reported the presence of increased RAGE expression in the spinal cord of early symptomatic hSOD1^{G93A} mice. We now present evidence of increased RAGE expression in the spinal cord of two other ALS mouse models (TDP-43^{Q331K} and TDP-43^{A315T}), suggesting the potential involvement of RAGE signaling beyond mutant SOD1-linked ALS. To evaluate the relevance of RAGE signaling in ALS pathology we tested the effect of FPS-ZM1, a previously described RAGE pharmacological inhibitor with the ability to cross the blood-brain barrier, on the onset and progression of the disease in hSOD1^{G93A} mice. Male and female hSOD1^{G93A} mice were randomly assigned into vehicle and FPS-ZM1 (1 mg/kg) treatment cohorts. Treatment started at the age of 60 days by daily i.p. injections. We observed no significant effect of the drug in the disease onset or survival of hSOD1^{G93A} mice when both genders were combined in the analysis. However, when compared with vehicle-treated mice, mice treated with FPS-ZM1 showed improved grip-strength for several weeks after disease onset. We also observed a significant delay in the age at which female hSOD1^{G93A} mice on FPS-ZM1 treatment exhibited 5% or 10% weight loss. These results suggest that RAGE inhibition could potentially have a beneficial effect only at early stages of the disease.

Disclosures: M. Pehar: None. **L. Liu:** None. **K.M. Killoy:** None. **S. Grauzam:** None. **M.R. Vargas:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.10/F23

Topic: C.06. Neuromuscular Diseases

Support: Charles H. Smith Endowment Fund to Gong Chen

Title: A gene therapy approach to directly reprogram reactive astrocytes into functional motor neurons in SOD1^{G93A} ALS mouse model

Authors: *M. PAN, Y. LIU, A. REDILLA, C. KERSTETTER, G. CHEN;
Huck Inst. of Life Sci., University Park, PA

Abstract: Amyotrophic lateral sclerosis (ALS) is an adult-onset, irreversible neurodegenerative disease, characterized by loss of motor neurons in the spinal cord, brain stem, and motor cortex, resulting in progressive muscle weakness, paralysis, and death within 3-5 years after diagnosis. There is no effective therapy available to halt the disease progression or provide a cure. Therefore, exploration of a new therapy is urgently needed. Our lab has pioneered an *in vivo* neuroregeneration technology to directly convert endogenous reactive glial cells into functional neurons after injury or diseases. Here, we develop a novel strategy to directly convert reactive astrocytes into functional motoneurons in the spinal ventral horn of SOD1^{G93A} ALS mouse model through adeno-associated virus (AAV)-based gene therapy. AAV-treated SOD1^{G93A} mice showed increased number of motoneurons in the spinal cord and significant improvement of motor functions in multiple behavioral tests. This gene therapy approach also extended the lifespan and delayed hindlimb paralysis in the SOD1^{G93A} mice. Our findings suggest that regenerating motoneurons from internal glial cells might lead to an innovative therapeutic treatment for ALS through replenishing the lost motoneurons and restoring the lost motor functions.

Disclosures: M. Pan: None. **Y. Liu:** None. **A. Redilla:** None. **C. Kerstetter:** None. **G. Chen:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.11/F24

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant P30GM114736
Nemours Foundation
University of Delaware Graduate Scholars Award

Title: Effect of inhibition of sodium/proton exchanger 5 (NHE5) on the alternative splicing of survival motor neuron 2 (SMN2)

Authors: S. KANDA[1], E. MOULTON[2], ***M. E. R. BUTCHBACH**[2,1,3];
[1]Biol. Sci., Univ. of Delaware, Newark, DE; [2]Nemours Biomed. Research/A. I. duPont Hosp. For Children, Wilmington, DE; [3]Pediatrics, Thomas Jefferson Univ., Philadelphia, PA

Abstract: Spinal muscular atrophy (SMA) is an autosomal recessive pediatric-onset neurodegenerative disease caused by the loss of spinal motor neurons which leads to generalized muscle atrophy. SMA is caused by mutations or the loss of *survival motor neuron 1* (SMN1). The human genome contains a duplicate copy of *SMN1* known as *SMN2*. The major difference between these genes is a cytosine to thymine (C-to-T) transition located in an exonic splicing enhancer (ESE) element within exon 7. The majority of the *SMN2* mRNA transcripts lack exon 7 (SMNΔ7) forming a truncated and unstable SMN protein. Since *SMN2* copy number is inversely related to disease severity, it is a well-established target for SMA therapeutics development. 5-(N-ethyl-N-isopropyl)-amiloride (EIPA), an inhibitor of sodium/proton exchangers (NHEs), has previously been shown to increase exon 7 inclusion and SMN protein levels in SMA cells. In this study several NHE inhibitors were evaluated for their ability to modulate *SMN2* expression. EIPA as well as 5-(N, N-hexamethylene)-amiloride (HMA) increase exon 7 inclusion in *SMN2* splicing reporter lines as well as in SMA fibroblasts. EIPA and HMA are more selective at inhibiting the NHE5 isoform than other NHE inhibitors. NHE5 is expressed in fibroblasts as well as in neuronal cells. Knockdown of *NHE5* also increases *SMN2* exon 7 inclusion in SMA cells. These results show that NHE5 inhibition increases *SMN2* expression and may be a novel target for therapeutics development.

Disclosures: M.E.R. Butchbach: None. **S. Kanda:** None. **E. Moulton:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.12/F25

Topic: C.06. Neuromuscular Diseases

Support: Institutional

Title: Scalable cGMP compliant expansion of human fetal and iPSC derived neural progenitor cells

Authors: A. FULTON, A. LAPERLE, *G. LAWLESS, K. ROXAS, P. AVALOS, C. SVENDSEN;
Cedars Sinai Med. Ctr., Los Angeles, CA

Abstract: Transplanted human fetal-derived neural progenitor cells have been used to treat multiple neurodegenerative diseases with mixed success. Early attempts engrafted primary fetal tissue in the striatum of Parkinson's disease patients to restore dopamine production. More recently, fetal-derived neural progenitors were engineered to produce glial cell line-derived neurotrophic factor (GDNF). These cells and were used in a completed Phase 1/2a trial delivering the cells to the spinal cord of ALS patients as a first ever cell and gene therapy.

Traditionally, such neural progenitor cells are expanded as either a monolayer or in suspension as aggregate cultures. Single cell passaging of either culture modality is not ideal as this passage method can lead to early cell senesce, which limits expansion potential, or can induce the cells to differentiate. Mechanical chopping has been successfully used to expand both fetal and iPSC-derived neural progenitor cells to scales suitable for early phase clinical trials. However, this method is time-consuming, labor-intensive, and challenging to implement at larger scales. We have developed a novel in-line passaging technique that maintains the expansion rate and cellular identity of mechanical chopping but that is faster, scalable, and can be implemented in a fully sealed system. Fetal and iPSC-derived neural progenitor cells produced with this new method maintain similar growth rates to cells expanded under traditional mechanical chopping methods. These cells also transplant efficiently in the spinal cord of nude rats, where they are safe for up to 3 months. This novel in-line mechanical passaging method will permit expansion of fetal and iPSC-derived aggregate cultures to scales necessary for later stage clinical trials and full therapeutic production.

Disclosures: **A. Fulton:** None. **A. Laperle:** None. **G. Lawless:** None. **K. Roxas:** None. **P. Avalos:** None. **C. Svendsen:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.13/F26

Topic: C.06. Neuromuscular Diseases

Support: Institutional Support

Title: iPSC derived neural progenitor cells genetically engineered to express GDNF can engraft and provide neuroprotection in the SOD1 ALS rat spinal cord

Authors: *A. H. LAPERLE, **G. LAWLESS**, A. FULTON, K. ROXAS, P. AAVLOS, V. J. GARCIA, C. N. SVENDSEN;
Cedars-Sinai Regenerative Med. Inst., Los Angeles, CA

Abstract: Amyotrophic Lateral Sclerosis (ALS) is a debilitating neurodegenerative disease affecting approximately 30,000 individuals in the US at any given time. Currently there are only two FDA approved drugs used to treat the disease, Edaravone and Riluzole, both of which slow progression only slightly. Promising preclinical treatments have included transplantation of supportive glial cells and delivery of glial cell line-derived neurotrophic factor (GDNF). Our group has generated and extensively characterized human fetal-derived neural progenitor cells that can differentiate into astrocytes and that can be transfected with lentivirus to stably produce GDNF. These GDNF-producing cells engraft efficiently in the spinal cord and slow the loss of

ChAT+ motor neurons in the SOD1 ALS rat. These cells have been banked under cGMP and we just completed a Phase 1/2a trial delivering the cells to the spinal cord of ALS patients as a first cell and gene therapy. While promising, the scalable use of fetal-derived neural progenitor cells is limited by the availability of starting material and a limited expansion potential. Further, the lentiviral transduction used to induce GDNF expression in these cells results in a heterogeneous population with varying copy number and GDNF production levels. To address these challenges, we have developed scalable, cGMP-applicable neural progenitor cell lines derived from human induced pluripotent stem cells (iPSCs). These iPSC-derived cells engraft efficiently in the ALS rat spinal cord and provide neuroprotection to diseased motor neurons, similar to the fetal-derived cells used in our clinical trial. Taking advantage of the clonal expansion capabilities of iPSCs, we generated clonal lines with a single copy GDNF construct inserted in the AAVS1 safe landing site. These lines uniformly express and produce GDNF. We also used this approach to generate iPSC-derived neural progenitor cell lines with more sophisticated constructs including a tetracycline-inducible promotor for regulated GDNF expression. These inducible expression systems could permit tailoring of GDNF dose to individual patients and present the added safety feature of turning off GDNF expression if required. These new iPSC-based lines are scalable to clinically relevant production volumes, uniformly produce GDNF, are safe for up to three months *in vivo,* and represent a promising new combination therapy for ALS.

Disclosures: **A.H. Laperle:** None. **G. Lawless:** None. **A. Fulton:** None. **K. Roxas:** None. **P. Aavlos:** None. **V.J. Garcia:** None. **C.N. Svendsen:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.14/F27

Topic: C.06. Neuromuscular Diseases

Support: CIRM Grant CLIN2-09284

Title: Human neural progenitor cells secreting glial cell line-derived neurotrophic factor (CNS10-NPC-GDNF) for the treatment of amyotrophic lateral sclerosis (ALS) - Clinical trial update

Authors: *P. AVALOS[1], K. ROXAS[1], P. ALLRED[2], H. BABU[2], C. PATIL[2], J. P. JOHNSON[2], R. H. BALOH[2], C. N. SVENDSEN[1];
[1]Regenerative Med. Inst., [2]Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal, progressive neurodegenerative disease characterized by rapid loss of muscle control and eventual paralysis. Symptoms result primarily from the death of spinal and cortical motor neurons. The annual incidence for ALS in developed

countries ranges from 0.4 to 2.4 per 100,000 individuals. ALS is typically lethal within 3-5 years of onset. Treatment is largely symptomatic and focused on improving quality of life. Currently, the only two FDA-approved treatments, riluzole and edaravone, have a limited effect on this devastating disease. Therefore, ALS is an ideal candidate for novel gene and cell therapy approaches. There is strong evidence that following an initial trigger within the motor neurons, further decline in their health is modulated by diseased astrocytes. Critically, the presence of healthy astrocytes can support dying motor neurons. Additionally, the growth factor, glial cell line-derived neurotrophic factor (GDNF), is able to protect dying motor neurons. The challenge is that targeted delivery of new astrocytes or beneficial growth factors to the central nervous system is difficult, as they do not penetrate the blood brain/spinal cord barrier. Human neural progenitor cells genetically modified to stably secrete GDNF (CNS10-NPC-GDNF) can be transplanted into the lumbar spinal cord, where they migrate into areas of motor neuron degeneration, mature into new supportive astrocytes and release GDNF leading to motor neuron protection. Therefore, a CIRM funded, 18 subject Phase 1/2a, single-center, blinded (as to side of injection), safety study of two escalating doses of CNS10-NPC-GDNF delivered unilaterally to the lumbar region of ambulatory ALS patients with moderate leg involvement is being performed under an active IND (Clinicaltrials.gov NCT02943850). The trial has a unique design in that CNS10-NPC-GDNF were injected unilaterally into the lumbar spinal cord, allowing the contralateral side to serve as an internal control. Although the primary objective is to assess the safety and tolerability of two doses of CNS10-NPC-GDNF, secondary outcome measures, including muscle strength, nerve conductivity tests and MRI, are being performed during the study period for preliminary signs of efficacy. At this time all subjects have been enrolled into the trial and received CNS10-NPC-GDNF treatment. This presentation will give an update of this ongoing clinical trial.

Disclosures: **P. Avalos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cedars-Sinai Medical Center. **K. Roxas:** None. **P. Allred:** None. **H. Babu:** None. **C. Patil:** None. **J.P. Johnson:** None. **R.H. Baloh:** None. **C.N. Svendsen:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.15/F28

Topic: C.06. Neuromuscular Diseases

Support: NIH 1R01AG051470
NIH P20 GM103418
NIH COBRE P30GM103326

Title: Applying human umbilical cord derived mesenchymal stem cells for the treatment of amyotrophic lateral sclerosis

Authors: T. MATSUDA[1], Y. BADAWI[1], K. SILVA[4], R. SODER[2], R. BAROHN[3], T. YOSHIDA[4], *H. NISHIMUNE[1];
[1]Anat. and Cell Biol., [2]Midwest Stem Cell Therapy Ctr., [3]Neurol., Univ. of Kansas Sch. of Med., Kansas City, KS; [4]Med. and Med. Pharmacol. and Physiol., Univ. of Missouri Sch. of Med., Columbia, MO

Abstract: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by a gradual loss of motor neurons that leads to paralysis and death. Studies indicate that neuromuscular junction (NMJ) denervation occurs in the early stages of the disease while neuronal cell bodies in the spinal cord remain intact. It is important to elucidate the molecular mechanisms that lead to NMJ denervation in ALS and identify interventions to improve neuromuscular function in ALS patients. We found that the synapse organizer laminin β2 decreases in NMJs of ALS model $SOD1^{G93A}$ mice, and transgenic expression of laminin β2 in skeletal muscles of $SOD1^{G93A}$ mice ameliorates NMJ denervation. In this study, we evaluated a stem cell-based therapy in $SOD1^{G93A}$ mice by using stem cells as vectors to express and secrete proteins that promote NMJ maintenance and are neurotrophic. The objectives of this study are (1) to determine whether human umbilical cord-Wharton's jelly derived mesenchymal stem cells (hMSCs) from multiple donors secrete synapse organizer laminin β2 and neurotrophic factors at similar levels, and (2) to evaluate hMSCs derived from different donors in vivo in $SOD1^{G93A}$ mice for NMJ maintenance and life-span extension. We discovered that hMSCs derived from multiple donors can increase the secretion of laminin β2 and neurotrophic factors by stimulation in media supplemented with growth factors. Furthermore, we confirmed that unilateral injection of hMSCs increased NMJ innervation rates and average myofiber cross sectional area in MSC-injected muscles compared to non-injected contralateral muscles. Then, the hMSCs obtained from two donors were transplanted separately into $SOD1^{G93A}$ mice by combined intrathecal and bilateral intramuscular injections. We analyzed hMSCs' survival length in the muscle after injection using immunohistochemistry. Importantly, injection of hMSCs obtained from the two donors improved neuromuscular function of injected $SOD1^{G93A}$ mice, and prolonged the lifespan of $SOD1^{G93A}$ mice compared to the vehicle injected $SOD1^{G93A}$ mice. Thus, injection of hMSCs obtained from donors could be an efficient treatment method to reduce NMJ denervation and improve the quality of life of ALS patients.

Disclosures: **T. Matsuda:** None. **Y. Badawi:** None. **K. Silva:** None. **R. Soder:** None. **R. Barohn:** None. **T. Yoshida:** None. **H. Nishimune:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

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Program #/Poster #: 475.16/F29

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant 1RO1NS078214
NIH Grant 1RO1AG051470
NIH P20 GM103418

Title: Degeneration of ALS mouse neuromuscular junctions analyzed using super resolution microscopy and ameliorated using human mesenchymal stem cells

Authors: *Y. BADAWI[1], S. TUNGTUR[2], T. TANAKA[1], R. SODER[4], R. BAROHN[3], K. SHIGEMOTO[5], H. NISHIMUNE[1];
[1]Anat. and Cell Biol., Univ. of Kansas Sch. of Med., Kansas City, KS; [2]Anat. and Cell Biol., Univ. of Kansas Sch. of Med., Kansas CIty, KS; [3]Neurol., Univ. of Kansas Sch. of Med., Kansas City, KS; [4]Midwest Stem Cell Therapy Ctr., Kansas City, KS; [5]Tokyo Metropolitan Inst. of Gerontology, Tokyo, Japan

Abstract: Presynaptic active zones play an essential role as synaptic vesicle release sites for synaptic transmission. In our previous studies, we identified the mechanism for active zone organization at mammalian NMJs that involves the interaction of muscle-derived synapse organizer laminin β2 with presynaptic voltage-gated calcium channels (VGCC). In this study, stimulated emission depletion (STED) super resolution microscopy analysis supports our molecular mechanism suggesting that laminin β2 anchors PQ-type VGCCs in front of postsynaptic junctional folds. PQ-type VGCC can then function as a scaffolding protein for active zone–specific proteins. Based on the knowledge obtained from wild-type NMJs, we evaluated the active zone proteins in NMJs of amyotrophic lateral sclerosis (ALS) mouse models. ALS is a neurodegenerative disorder in which NMJ denervation occurs before the death of motor neuron cell bodies in the spinal cord, suggesting a “dying-back” neuropathy. The mechanisms underlying NMJ denervation in ALS remain unknown. The pathogenesis of ALS may involve changes in protein levels, which are important for the maintenance of NMJ active zones and regulation of neurotransmission. For this purpose, we analyzed active zone proteins in NMJs of $SOD1^{G93A}$ mice, a rodent ALS model, at an early, pre-symptomatic stage (P85) and a symptomatic stage (P140). Interestingly, we found that the quantity of active zone proteins Bassoon, Piccolo, and PQ-type VGCC decreased in innervated NMJs of ALS mice compared to age- and sex-matched wild-type mice. We also found that laminin β2 level decreased in $SOD1^{G93A}$ mice and transgenic expression of laminin β2 in $SOD1^{G93A}$ mice ameliorated NMJ denervation. These results suggest that the level of laminin β2 protein is critical for the

maintenance of NMJs in ALS patients. As a therapeutic source of laminin β2, we evaluated stem cells as vectors to express and secrete proteins that promote NMJ maintenance and are neuroprotective. We identified that stimulating human mesenchymal stem cells (hMSCs) in media supplemented with growth factors can increase laminin β2 and neurotrophic factor secretion. Transplanting the stimulated hMSCs in $SOD1^{G93A}$ mice maintained NMJ innervation and prolonged $SOD1^{G93A}$ mice survival. This could prove to be an efficient and a long-term delivery system for laminin β2 to reduce NMJ denervation and increase the quality of life of ALS patients.

Disclosures: Y. Badawi: None. **S. Tungtur:** None. **T. Tanaka:** None. **R. Soder:** None. **R. Barohn:** None. **K. Shigemoto:** None. **H. Nishimune:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.17/F30

Topic: C.06. Neuromuscular Diseases

Support: ALS Canada-Brain Canada Hudson Translational Team Grant

Title: Peptide-directed selective knockdown of misfolded SOD1 as a therapy for amyotrophic lateral sclerosis

Authors: *T. ZHOU[1], T. GUAN[1], Y. WANG[2], H. MARZBAN[1], J. KONG[1];
[1]Univ. of Manitoba, Winnipeg, MB, Canada; [2]Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease, in which misfolded SOD1 (superoxide dismutase 1) plays a central role of pathogenesis. Targeting misfolded SOD1 is therefore a rational approach towards a cure for ALS. Here we present a new approach to selectively knockdown misfolded SOD1 by insertion of the CT-4 epitope of Derlin-1 into the chaperone-mediated autophagy system. In this study, we report efficiency and specificity of CT-4 peptide in knocking down misfolded SOD1 *in vitro* and *in vivo*. Our results revealed that CT-4 treatment resulted in a selective degradation of misfolded SOD1 in a dose-, time- and lysosomal activity-dependent manner *in vitro*. The *in vivo* studies revealed that CT-4 treatment resulted in knockdown of misfolded SOD1 in the tissues from G93A transgenic mouse model of ALS. In addition, our daily injection of CT-4 peptide significantly delays disease onset and extends lifespan of G93A transgenic mice of ALS. Furthermore, we explored the potential mechanism underlying which CT-4 peptide delays disease onset. Our data indicated that knockdown of misfolded SOD1 could directly affect MCT1 protein expression in SC, suggesting that CT-4 peptide treatment results in preservation of MCT1 expression, maintenance of axon

myelin and protection of neurons in ALS animal model. Therefore, the peptide may be developed into a cure for ALS.

Disclosures: **T. Zhou:** None. **T. Guan:** None. **Y. Wang:** None. **H. Marzban:** None. **J. Kong:** None.

Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.18/F31

Topic: C.06. Neuromuscular Diseases

Support: The Robert Packard Center for ALS Research at Johns Hopkins

Title: Investigating Cx43 HC and GJ localization and function in amyotrophic lateral sclerosis

Authors: *J. A. JOSEPH[1], M. L. GALLARDO[2], A. A. ALMAD[3], A. POKHAREL[1], S. GROSS[1], A. TAGA[1], J. CONTRERAS[2], N. MARAGAKIS[1];
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Abstract: Connexin 43 (Cx43) is the most ubiquitous connexin in the central nervous system and forms hemichannels (HC) and gap junctions (GJ) in astrocytes. Increases in Cx43 expression and activity are observed in neurodegenerative diseases including Alzheimer's and Parkinson's. Our lab recently reported that Cx43 upregulation in astrocytes contributes to motor neuron (MN) toxicity in Amyotrophic Lateral Sclerosis (ALS). We demonstrated that astrocyte expression of Cx43 is increased in frontal cortex and spinal cords of ALS patients and in the $SOD1^{G93A}$ ALS mouse model, and that $SOD1^{G93A}$ astrocyte mediated MN toxicity was in part due to Cx43 HCs. Given $SOD1^{G93A}$ astrocytes incite disease progression but not onset, this suggests astrocytes, and potentially Cx43, play a key role in disease propagation. In the majority of patients disease propagation occurs in contiguous anatomic regions over time, but out lack of understanding fundamentally limits the design of disease modifying therapies after diagnosis. We aim to understand the role of Cx43 in ALS disease spread using a novel triple transgenic $SOD1^{G93A}$;GFAP-Cre;$Cx43^{fl/fl}$ mouse and human ALS induced pluripotent stem cell (hiPSC) models to examine Cx43 HC localization and function.
In order to determine the ratio of Cx43 HC to total Cx43, we employed a published method to pulldown HCs in vitro. This technique utilizes biotin binding on lysine residues of Cx43 HC extracellular domains, then biotin-streptavidin binding to pulldown proteins and blot for Cx43. We then determine the percentage of Cx43 HCs to total Cx43 using total protein linear modeling described by Retamal et al. We performed this in ALS hiPSC astrocyte cultures using six patient lines, including controls, sporadic, and familial lines. We also used qPCR to test toxicity profiles

of WT, disease, and the triple transgenic mouse astrocytes.
Our data suggest total Cx43 is dramatically increased in $SOD1^{G93A}$ astrocytes, including Cx43 HC levels. Interestingly, the ratio of Cx43 HC to total Cx43 expression in this model is increased and suggests a greater percentage of Cx43 HC exists on the membrane. Initial studies using ALS hiPSC-derived astrocytes show similar increases in Cx43 expression and HC localization. qPCR data show the $SOD1^{G93A}$ astrocyte-mediated toxicity is not related to the A1 toxicity phenotype. Disease astrocytes and Cx43 KO disease astrocytes have similar profiles despite the lack of Cx43 expression.
Cx43 is a novel protein associated with ALS disease progression and the mechanism of HC toxicity has yet to be explored. Using novel models, our findings shed light on a potential role for Cx43 HC in ALS and as a potential therapeutic target.

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Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.19/F32

Topic: C.06. Neuromuscular Diseases

Support: NIH Grant R01NS089640

Title: Nicotinamide riboside modestly extends survival in ALS-linked mutant $hSOD1^{G93A}$ mice

Authors: B. A. HARLAN, K. M. KILLOY, M. PEHAR, *M. R. VARGAS;
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Abstract: Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease, caused by the progressive degeneration of motor neurons in the spinal cord, brain stem, and motor cortex. Approximately 10-20% of familial ALS is caused by a toxic gain-of-function induced by mutations of the Cu/Zn-superoxide dismutase (SOD1). Nicotinamide adenine dinucleotide (NAD^+) is an essential redox molecule and a key player in several signaling pathways that govern fundamental biological processes. Activation of NAD^+-dependent signaling pathways has a major effect in the capacity of the cell to modulate mitochondrial function and counteracts the deleterious effects of increased oxidative stress. We have previously shown that increasing NAD^+ availability improves antioxidant defenses and abrogates the neurotoxicity of ALS-astrocytes towards co-cultured motor neurons. Nicotinamide riboside (NR) can serve as an NAD^+ precursor and effectively increases total NAD^+ content in different cell types and tissues. Here we explore the role of an NR supplemented diet in the ALS-like pathology displayed by mice expressing the ALS-linked mutant $hSOD1^{G93A}$. We found that NR

modestly extends the survival of hSOD1^{G93A} mice, decreases reactive gliosis in the spinal cord and appears to confer increased metabolic flexibility in the skeletal muscle. Our results suggest that modulating NAD^+ availability could be a potential therapeutic strategy in ALS.

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Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.20/F33

Topic: C.06. Neuromuscular Diseases

Title: Aberrant assembly machine modulators: A novel approach to ALS diagnostics and therapeutics

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Abstract: The mislocalization of proteins has been recognized as a hallmark of many neurodegenerative diseases. Our prior work on host-catalyzed viral assembly led to the discovery of multi-protein complex (MPC) “assembly machines” playing previously unappreciated roles in protein homeostasis. Assembly machines cannot easily be detected by conventional proteomics, in part due to their transience/lability. However, these targets are druggable if you can figure out how to detect them, which is what we have done. Remarkably, some of the small-molecule chemotypes have robust activity against both TDP-43 mislocalization as well as on stress-induced TDP-43 aggregation, and in both sporadic and familial ALS cellular models. TDP-43 and Ran GTPase proteins that are implicated in ALS pathophysiology was detected as part of the assembly machine. The most advanced compounds demonstrate *in vivo* protection against motor neuron degeneration by a variety of metrics in transgenic *C. elegans* (TDP-43 A315T), *D. melanogaster* (C9orf72 repeat expansion), and mouse (SODG93A) ALS models. Evidence for distinctive aberrant assembly machine target engagement is observed in both SOD G93A transgenic mouse brain and in sporadic ALS patient-derived fibroblasts by use of drug resin affinity chromatography (DRAC) to identify the proteins comprising ALS-involved normal and aberrant assembly machines. These tools also correlate findings in cells to activity of the drugs, and, using peripheral blood mononuclear cells (PBMCs), identify specific patient subsets of the

ALS phenotype which respond best to a given assembly modulator. Taken together, our findings support the hypothesis that in many cases ALS is a disease of assembly machine dysfunction correctable by small molecule allosteric site-targeted assembly modulators. This suggests a new conceptual lens - catalyzed assembly modulation - through which to view ALS pathophysiology. We have established tools that have practical application to better understand the molecular basis for ALS and at the same time be used in clinical trial patient selection, and objective assessment of therapeutic efficacy. Compounds to these distinctive novel targets correct molecular defects in ALS and are being advanced in a manner that may allow individualization of therapy for patient subsets defined by peripheral DRAC signatures. These signatures are predicted to appear very early in disease pathogenesis, perhaps even prior to onset of clinical symptoms and aid in the reversal of ALS disease course.

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Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.21/F34

Topic: C.06. Neuromuscular Diseases

Support: ALS Association
NSERC Grant
CIHR Vanier Canada Graduate Scholarship
Research Manitoba Graduate Studentship

Title: Raltegravir effectively reverses ERVK integrase-mediated pathology

Authors: *D. L. DI CURZIO[1], M.-J. NADEAU[1], B. MEEK[1], M. GURM[2], R. DOUVILLE[1,2]; [1]Biol., Richardson Col. for the Envrn. & Sci. Complex, Univ. of Winnipeg, Winnipeg, MB, Canada; [2]Immunol., Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: Endogenous retroviruses embody over 8% of the human genome, with endogenous retrovirus-K (ERVK) being the most intact and biologically active ERV. ERVK has been shown to have biological roles in health and disease, including various cancers, Human

Immunodeficiency Virus (HIV) infection, and Amyotrophic Lateral Sclerosis (ALS). ERVK encodes an integrase (IN) enzyme, a class of retroviral enzymes known to cause DNA damage during integration of viral DNA into host genomes. Since genomic instability and immune impairment are hallmark pathological findings in ALS, we hypothesized that the ERVK IN enzyme contributes to neuropathology in ALS. Our aim was to determine if the IN inhibitor Raltegravir reverses ERVK IN pathology. We examined levels of DNA damage, expression of innate antiviral protein interferon regulatory factor 3 (IRF3), and cell death in human astrocytes (SVGA cells) overexpressing ERVK IN and *ex vivo* human motor cortex and spinal cord tissue using immunohistochemical techniques. Western blot was also used to examine these pathological changes in ERVK IN-transfected SVGAs. Raltegravir treatment was performed on the transfected astrocytes to examine the therapeutic effects of ERVK IN inhibition. In comparison to neuronormal (NN) controls, patients with ALS exhibit enhanced ERVK IN expression in the motor cortex and spinal cord, along with increased levels of the modified histone and DNA damage marker, γH2AX, and necroptosis cell death marker, MLKL. Cytoplasmic IRF3 aggregates and impaired IRF3 nuclear translocation were also found in $ERVK^+$ cells in ALS motor cortex compared to NN controls. ERVK IN-transfected SVGAs showed perinuclear and nuclear aggregates of ERVK IN along with nuclear accumulation of DNA damage marker γH2AX, which occurred in conjunction with aberrant perinuclear deposition of DNA repair protein BRCA1. SVGA cells co-transfected with ERVK IN and constitutively active IRF3 showed cytoplasmic IRF3 sequestration, which prevented nuclear translocation of IRF3. Raltegravir treatment of ERVK IN expressing SVGAs reduced γH2AX foci, overall levels of ERVK IN, and IRF3 translocation to the nucleus was restored. The ERVK IN enzyme drives DNA damage, impairs DNA repair, and suppresses innate antiviral immunity. Together, these molecular mechanisms may contribute to neuropathology in ALS. ERVK IN-driven pathology is reversed by HIV IN inhibitor drug Raltegravir. FDA-approved integrase inhibitors, such as Raltegravir, may confer therapeutic benefit in ALS.

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Poster

475. Motor-Neuron Disease: Therapeutics

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 475.22/F35

Topic: C.06. Neuromuscular Diseases

Support: Motor Neurone Disease Association (Grant April16/848-791)

Title: Beneficial effects of mesenchymal stem cell-derived exosomes and of exosome-shuttled microRNAs on the activated phenotype of mouse and human-derived astrocyte cell cultures in amyotrophic lateral sclerosis

Authors: *G. B. BONANNO[1,3,4], F. PROVENZANO[1], M. BALBI[1], S. NYBERG[5], L. FERRAIUOLO[5], C. MARINI[2], B. PARODI[2], D. GIUNTI[2], T. BONIFACINO[1], N. KERLERO DE ROSBO[2], C. USAI[6], M. MILANESE[1,3], A. UCCELLI[2,3,4], P. J. SHAW[5];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease affecting motor neuron (MN) viability Degeneration of MNs has been linked to neuroinflammation, supported mostly by activated microglia and astrocytes. We have shown that intravenous administration of mesenchymal stem cells (MSCs) to the $SOD1^{G93A}$ mouse model of ALS prolonged survival, ameliorated motor skills and reduced inflammation in the spinal cord (Mol Med 18: 794, 2012). These beneficial effects were not associated with MSC differentiation and we postulated that they were due to paracrine mechanisms. As possible paracrine mechanisms supporting the MSC effects, we studied here the activity of IFNγ-primed MSC-derived exosomes and exosome-shuttled miRNAs on spinal cord astrocyte cultures from 120 day-old symptomatic $SOD1^{G93A}$ mice or on human iNPC-derived astrocytes from sporadic and familial ALS patients,. Twenty four hours exposure of symptomatic $SOD1^{G93A}$ mouse-derived astrocytes to MSCs-produced exosomes significantly reduced the overexpression of the astrogliosis markers GFAP and vimentin and of the neuroinflammatory marker NLRP3. $SOD1^{G93A}$ astrocytes were characterized by increased expression and release of the pro-inflammatory cytokines IL1β, TNFα e IL6. These alterations were strongly reduced after exosome exposure. To verify the impact of astrocyte treatment with exosomes on MN viability, spinal MNs from $SOD1^{G93A}$ embryos were co-cultured with exosome-treated or control astrocytes. Viability of MNs was increased when co-cultured with exosome-treated astrocytes. We also tested the effects of transfecting $SOD1^{G93A}$ astrocytes with mimics of 9 miRNAs, which have been found up-regulated in MSCs and present in exosomes. Seven out of 9 miRNA mimics affected the reactive phenotype of astrocytes by significantly decreasing the overexpression of GFAP, IL1β and TNFα. Finally, we verified the effects of human MSC(hMSC)-derived exosomes on iNPC-derived astrocytes (iAstrocytes) from SOD1 or C9orf72-mutants and sporadic ALS patients. hMSCs-derived exosomes activated the p62-Nrf2-NQO1 antioxidant pathway in iAstrocytes. The amelioration of iAstrocyte phenotype by hMSCs-derived exosomes translated into a direct rescue of iAstrocyte-mediated neuron toxicity. Thus, exosomes derived from primed-MSCs, and their miRNAs cargo, are able to modulate the neuroinflammatory and antioxidant pathways in reactive ALS-astrocytes. These effects have a direct positive impact on spinal MN viability and pave the way to translational preclinical in-vivo studies.

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Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.01/F36

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Long-term voluntary physical exercise exerts neuroprotective effects and alleviates subsequent akinesia and gait disturbance in a rat model of Parkinson's disease

Authors: *W.-L. TSAI[1], C.-W. KUO[2], Y.-H. CHEN[3], Y.-Z. HUANG[4], Y.-T. HUANG[5], C.-W. HSU[5], S.-C. HSUEH[1], J.-H. LAI[1], Y.-H. CHIANG[1], C.-F. CHANG[6], T.-J. KAO[1], T.-H. HSIEH[5]; [1]Taipei Med. Univ., Taipei, Taiwan; [2]Natl. Taiwan Univ., Taipei, Taiwan; [3]Tri-Service Gen. Hospital/National Def. Medi, Taipei, Taiwan; [4]Chang Gung Mem. Hospital/Chang Gung Univ., Taoyuan, Taiwan; [5]Chang Gung Univ., Taoyuan, Taiwan; [6]Taipei City Hospital, Zhongxiao Br., Taipei, Taiwan

Abstract: Background: Parkinson's disease (PD) is the second most prevalent neurodegenerative disorders affecting 7-10 million individuals. The pathologic hallmark of PD is a loss of nigrostriatal dopaminergic neurons, leading to several motor and non-motor disturbances, e.g. akinesia, gait disturbance, depression, and anxiety. Recent animal studies demonstrate that physical exercise improves the behavioral and neuropathological deficits in PD. However, the underlying mechanism is still unclear. In this study, we investigated whether long-term effects exercise have the neuroprotective effects in dopaminergic nigrostriatal neurons and further alleviate the impairment of gait pattern, locomotor activity, akinesia and anxiety in PD rats.
Methods: A hemiparkinsonian rat model, generated by unilateral injection of 6-hydroxydopamine (6-OHDA) into the medial forebrain bundle (MFB), was applied to evaluate the neuroprotective effects and motor behaviors. The comprehensive spatiotemporal gait analysis, open field locomotor activity, akinesia, apomorphine-induced rotational analysis as well as dopaminergic neurons degeneration level were assessed every week and up to 8 weeks after daily voluntary running wheel exercise.
Results: When compared with the sham-treated group, we found that 8 weeks of voluntary exercise significantly reduced the 6-OHDA induced motor deficits in gait pattern, locomotor activity, akinesia, rotational behavior, and anxiety. Immunohistochemically, tyrosine hydroxylase (TH)-positive neuron in the substantia nigra was significantly preserved in the exercise group.

Conclusions: Our results demonstrate that long-term exercise training is effective for neuroprotection and further attenuates motor declines induced by 6-OHDA in an experimental model of PD. Our data further highlight the potential therapeutic effects of long-term physical exercise that might be relevant to the clinical effect for the further potential application of human PD subjects.
Keywords: Parkinson's disease; gait disturbance, locomotor activity; running wheel exercise; Dopamine depletion

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Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.02/F37

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

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Fundamental Research Funds for the Central Universities #17817014
Programme of Introducing Talents of Discipline to Universities #B14036

Title: Decelerating photoreceptor degeneration by the flavonoid luteolin in a mouse model of retinitis pigmentosa

Authors: *A. LI[1], X. LIU[1], F. LIU[1], J. HUANG[2], Y. XU[1];
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Abstract: Retinitis pigmentosa (RP) is a hereditary retinal disease with progressively sequential losses of rods and cones that ultimately lead to blindness. The prevalence of RP is approximately 1/3500, whereas no effective treatment has been available so far. Luteolin as an important flavonoid derived from several herbs is known to exert antioxidant and anti-inflammatory effects, and yet its influence on RP is little explored. Here we examine whether luteolin mitigates the impairments of retinal morphology and function in rd10 mice, a slow photoreceptor-degeneration model of RP, and attempt to unmask the underlying mechanism. Luteolin or vehicle phosphate-buffered solution was intraperitoneally injected into rd10 mice daily from P14 to P25 when photoreceptor degeneration reaches peak. Immunohistochemistry, visual behaviors and electroretinogram were applied to assess the structure and function of retinas after the designated treatments. Intracellular levels of calcium ions and reactive oxygen species (ROS)

were measured fluorometrically. Quantitative polymerase chain reaction and protein array screening followed by western-blotting confirmation were used to identify the potential signaling pathways involved in this process. Compared to the sham control, luteolin significantly retained the normal retinal structure and increased the survival of photoreceptors in rd10 mice, accompanied with the improved visual behavioral performance and light responses at P25. Meanwhile, cytosolic calcium overload, ROS level elevation and photoreceptor apoptosis in rd10 mice were largely attenuated. Additionally, expression of pro-inflammatory cytokines after luteolin treatment was down-regulated, concurrent with the reduced immunoreactivity of glial fibrillary acidic protein in Müller cells, an indicator for the overall retinal inflammation. The above-mentioned beneficial effects of luteolin was likely mediated via the Jun N-terminal kinase (JNK) pathway given that inhibiting the phosphorylation of JNK diminished these biological alterations. Collectively, administration of luteolin helps to delay photoreceptor degeneration and subsequently maintains visual function in RP possibly through JNK pathway-mediated neuroprotection.

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Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.03/F38

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: BBSRC Grant BB/M009513/1

Title: MSC derived extracellular vesicles reduce hypoxia ischaemia induced perinatal brain injury

Authors: *C. SISA[1], J. NAYLOR[1], M. HERRERA SANCHEZ[2], S. KHOLIA[2], S. BRUNO[2], M. DEREGIBUS[2], G. CAMUSSI[2], J. M. INAL[3], S. LANGE[4], M. HRISTOVA[1];
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Abstract: Background: Neonatal hypoxic-ischemic (HI) insult is a leading cause of disability and death in newborns, with therapeutic hypothermia being the only currently available clinical intervention. Thus there is a great need for adjunct and novel treatments for enhanced or alternative post-HI neuroprotection. Extracellular vesicles (EVs) derived from mesenchymal stromal/stem cells (MSCs) have recently been shown to exhibit regenerative effects in various injury models. Here we present findings showing neuroprotective effects of MSC-derived EVs in the Rice-Vannucci model of severe HI-induced neonatal brain insult.**Methods:** Mesenchymal stromal/stem cell-derived EVs were applied intranasally immediately post HI-insult and

behavioral outcomes were observed 48 h following MSC-EV treatment, as assessed by negative geotaxis. Brains were thereafter excised and assessed for changes in glial responses, cell death, and neuronal loss as markers of damage at 48 h post HI-insult.**Results:** Brains of the MSC-EV treated group showed a significant decrease in microglial activation, cell death, and percentage tissue volume loss in multiple brain regions, compared to the control-treated groups. Furthermore, negative geotaxis test showed improved behavioral outcomes at 48 h following MSC-EV treatment.**Conclusion:** Our findings highlight the clinical potential of using MSC-derived EVs following neonatal hypoxia-ischaemia.

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Poster

476. Neuroprotective Mechanisms

Location: Hall A

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Program #/Poster #: 476.04/F39

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: BBSRC Grant BB/M009513/1

Title: Curcumin: Novel treatment in neonatal hypoxic-ischaemic brain injury

Authors: *E. ROCHA FERREIRA[1], **C. SISA**[2], S. BRIGHT[1], T. FAUTZ[1], M. HARRIS[1], I. CONTRERAS RIQUELME[1], C. AGWU[1], T. KURULDAY[1], D. HILL[1], S. LANGE[3], M. HRISTOVA[1];
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Abstract: Hypoxic-ischaemic encephalopathy (HIE) is a major cause of mortality and morbidity in neonates, with a global incidence of 3/1000 live births. HIE brain damage is associated with an inflammatory response and oxidative stress, resulting in the activation of cell death pathways. There is an unmet clinical need for the development of novel therapeutic interventions for the treatment of HIE. Curcumin is an antioxidant reactive oxygen species scavenger, with anti-tumour and anti-inflammatory activity. Curcumin has been shown to attenuate mitochondrial dysfunction, stabilise the cell membrane, stimulate proliferation, and reduce injury severity in adult models of spinal cord injury, cancer, and cardiovascular disease. The role of curcumin in neonatal HIE has not been widely studied due to its low bioavailability and limited aqueous solubility. This study aimed to investigate the effect of curcumin treatment in neonatal HIE, including time of administration and dose-dependent effects. Our results indicate that curcumin administration prior to HIE in neonatal mice elevated cell and tissue loss, as well as glial

activation compared to HI alone. However, immediate post-treatment with curcumin was significantly neuroprotective, reducing grey and white matter tissue loss, TUNEL+ cell death, microglia activation, reactive astrogliosis and iNOS oxidative stress when compared to vehicle-treated littermate controls. This effect was dose-dependent, with 200μg/g BW as the optimal dose-regimen and was maintained when curcumin treatment was delayed by 60min or 120min post-HI. Cell proliferation measurements showed no changes between curcumin and HI alone, suggesting that the protective effects of curcumin on the neonatal brain following HI are most likely due to curcumin's anti-inflammatory and antioxidant properties, as seen in the reduced glial and iNOS activity, and decrease of phosphorylated STAT3 Y705 and S727 protein levels. Also, curcumin-treated animals showed an increase in ipsilateral PHB, supporting its neuroprotective role as a mitoprotective and neuroprotective agent. In conclusion, this study suggests curcumin as a potent neuroprotective agent with potential for the treatment of HIE. The delayed application of curcumin further increases its clinical relevance.

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Poster

476. Neuroprotective Mechanisms

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Program #/Poster #: 476.05/F40

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: BBSRC BB/M009513/1

Title: Properdin a novel target for neuroprotection in neonatal hypoxic ischaemic brain injury

Authors: *M. H. HRISTOVA[1], C. SISA[2], Q. AGHA-SHAH[1], B. SANGHERA[1], A. CARNO[1], C. STOVER[3];
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Abstract: Hypoxic-ischaemic (HI) encephalopathy is a major cause of neonatal mortality and morbidity, with global incidence of 3 per 1000 live births. Intrauterine or perinatal complications, including maternal infection constitute a major risk for the development of neonatal HI brain damage. The mechanisms underlying the trigger of brain damage under the conditions of HI alone and infection-sensitised HI overlap, but also differ. During HI brain damage inflammatory response and oxidative stress occur, causing subsequent cell death. The presence of an infection however sensitises the neonatal brain making it more vulnerable to the HI damage. Currently, therapeutic hypothermia is the only clinically approved treatment

available for HI encephalopathy, however it is only partially effective in HI alone and ineffective in infection-sensitised HI. Therefore there is an unmet clinical need for the development of novel therapeutic interventions for the treatment of HI. Such an alternative is targeting the complement system. Absence of the classical pathway in the neonatal HI brain is neuroprotective, however there is paucity of data on the participation of the alternative pathway and in particular the role of properdin in HI brain damage. Our study aimed to validate the effect of global properdin deletion in two models: HI alone and LPS-sensitised HI thus addressing two different clinical scenarios. Our results indicate that global properdin deletion in a Rice-Vannucci model of neonatal HI and LPS-sensitised HI brain damage, in the short term, clearly reduced forebrain cell death and microglial activation, as well as tissue loss. In HI alone, deletion of properdin reduced TUNEL+ cell death and microglial post-HI response at 48h post insult. Under the conditions of LPS-sensitised HI, properdin deletion diminished TUNEL+ cell death, tissue loss and microglial activation at 48h post-HI. Overall, our data suggests a critical role for properdin, and possibly also a contribution in neonatal HI alone and in infection-sensitised HI brain damage. Thus, properdin can be considered a novel target for treatment of neonatal HI brain damage.

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Poster

476. Neuroprotective Mechanisms

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Grants from the Ministry of Education, Culture, Sports, Science, and Technology of Japan 18K05542

Title: Soy isoflavone daidzein but not genistein protects Neuro2a cells from oxidative stress via AMPK and mitochondrial enhancement

Authors: S. ITO[1], *K. NAGAI[2];
[1]Koshien Univ., Hyogo, Japan; [2]Dept. of Food and Nutr., Senri Kinran Univ., Osaka, Japan

Abstract: Oxidative stress is involved in most of the neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease. Although the antioxidative property of soy isoflavones was reported in different experimental models, it has been believed that the protection was achieved as antioxidants against reactive oxygen species rather than their effects in the cells. While typical soy isoflavones daidzein and genistein were reported to activate mitochondrial biogenesis regulator Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1α) via Sirt1 activation. Thus, we hypothesized that daidzein or

genistein attenuates oxidative stress induced cell damage via sirtuin activation followed by mitochondrial biogenesis. In this study, we studied whether daidzein and genistein can protect the neuronal cell line Neuro2a cells from oxidative stress via mitochondrial enhancement. We treated cells with sodium nitroprusside (SNP) as an oxidative stress model. At first, we analyzed if isoflavones actually show cell protective function against oxidative stress and increases intracellular mitochondria. Pretreatment with daidzein or genistein reduced SNP-induced cell death, and increased intracellular mitochondria evaluated by cytometric analysis stained with JC-1 even under oxidative stress condition. Then, we studied mechanisms of cell protection and mitochondrial biogenesis. Although in the previous report, isoflavones induced mitochondrial biogenesis via Sirt1 activation, sirtuin inhibition did not affects cell protection and mitochondrial biogenesis. Next, we focused on AMP-activated protein kinase (AMPK) which was reported to regulate PGC1α activity. In the presence of AMPK inhibitor dorsomorphin, effects of daidzein on cell protection and mitochondrial biogenesis were attenuated. However, effects of genistein were not affected by drosomorphine. Our data suggested that protective effects of daidzein but not genistein achieved via AMPK activation followed by PGC1α. Our data suggests that consumption of soy isoflavones reduces the risk of neurodegenerative diseases via affecting intracellular signaling and mitochondrial biogenesis.

Disclosures: **S. Ito:** None. **K. Nagai:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.07/F42

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Technical Supports Medical Institute of Bioregulation and the Research Support Center, Graduate School of Medical Sciences, Kyushu University.

Title: Gastrointestinal hormone-related neuroprotection induced by molecular hydrogen in Parkinson's disease model mice

Authors: *M. NODA, Y. UEMURA, T. NIIYAMA;
Pathophysiology, Grad. Sch. Pharm. Sci. Kyushu Univ., Fukuoka, Japan

Abstract: We have been investigating the protective and preventive effects of molecular hydrogen (H_2), as a new medical gas, in a model of Parkinson's disease (PD) [1]. The mechanisms of how H_2 works are still in debate but indirect effects of H_2 are suggested in case of chronic drinking H_2-containint water. It takes time and persists for at least a couple of days in a mouse model of PD [2]. The evidence that drinking H_2 water was the most effective way rather than inhaling H_2 in PD model animal led to the finding that H_2 induces ghrelin production and

release from the stomach by activating β1 adrenergic receptors. [3]. However, ghrelin may not the only factor mediating the beneficial effects of H_2. We still observed protective effects of H_2 in PD model mice using ghrelin-knock out (KO) mice [4], though we have not yet analyzed which factors are upregulated in ghrelin-KO mice, which are supposed to compensate the lack of ghrelin. To confirm the upregulation of ghrelin by H_2, we used stomach ghrelinoma (SG-1) cells. We treated SG-1 cells with H_2-containing medium, changing medium every day. We observed that ghrelin mRNA was significantly increased after 7 days, but not 1 or 3 days. The upregulation of ghrelin mRNA was not observed by treatment of noradrenalin (NA). On the other hand, the release of ghrelin from SG-1 cells was significantly stimulated by NA, but not by incubation with H_2 for 7 days.

Though the molecular mechanism of H_2-induced upregulation of ghrelin is still under investigation, the distinct mechanism due to the brain-stomach connection may help to understand the broad spectrum of H_2 function.

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Disclosures: M. Noda: None. **Y. Uemura:** None. **T. Niiyama:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.08/F43

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Inhibition of miRNA let7i enhance the progesterone-induced neuroprotection

Authors: *S. KIM[1], T. NGUYEN[2], M. SINGH[1];
[1]Cell and Mol. Physiol., Loyola Univ. Chicago Stritch Sch. of Med., Maywood, IL; [2]Pharmacol. and Neurosci., Univ. of North Texas Hlth. Sci. Ctr., Fort Worth, TX

Abstract: Our laboratory reported that the miRNA, let7i, increases as a function of ischemic injury (e.g., stroke), and that overexpression of let7i negatively regulates Pgrmc1 expression, disrupts progesterone (PROG)-induced BDNF release and reduces PROG's cytoprotective

effects. We also discovered that oxidative stress caused by H_2O_2 resulted in an increase in let7i expression in both C6 astrocyte glial and SH-SY5Y neuronal cell lines. These data provided insight into the possibility that inhibition of let7i expression may be a strategy to facilitate PROG's protective efficacy, especially against insults/ diseases in which oxidative stress plays a role (e.g., stroke, traumatic brain injury, and such neurodegenerative diseases such as Alzheimer's disease). Based on this, we hypothesized that let7i represses PROG's neuroprotective effects by down-regulating the expression of Pgrmc1, and therefore that inhibiting let7i could facilitate PROG-induced neuroprotection against oxidative insults. Our data revealed that overexpression of let7i in C6 astrocytes and differentiated SH-SY5Y cells decreased the expression of Pgrmc1 and also abolished the protective effect of PROG against H_2O_2-induced oxidative stress. Previously, using the middle cerebral artery occlusion (MCAo) model of stroke, applied to ovariectomized mice, we demonstrated that let7i inhibitor, delivered via intracerebroventricular (ICV) injection, enhanced the neuroprotective effects of PROG. Similarly, let7i inhibitor reversed the negative effect of miRNA let7i on PROG-induced protection against oxidative insults in both C6 astrocytes and SH-SY5Y neuronal cell lines. Collectively, these data support the potential role of let7i as a therapeutic target, whereby its inhibition can enhance PROG-induced cytoprotection. By extension, our data suggest that when considering the role of progesterone in protecting the brain against trauma and neurodegenerative diseases, simultaneous inhibition of let7i may be an important adjuvant therapy.

Disclosures: S. Kim: None. **T. Nguyen:** None. **M. Singh:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.09/F44

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Germinated brown rice reduced glutamate-induced apoptotic cell death in mouse hippocampal HT22 cell line

Authors: *E. M. OO[1], F. PADUNGRAKSART[4], C. TURBPAIBOON[1], L. KHOWAWISETSUT[2], P. UAWITHYA[3], V. CHAISUKSUNT[5], P. SOBHON[6], S. CHOMPOOPONG[1];
[1]Dept. of Anat., [2]Dept. of Parasitology, [3]Dept. of Physiol., Fac. of Med. Siriraj Hosp., Mahidol University, Bangkok, Thailand; [4]Dept. of Anat., Fac. of Med. Siriraj Hospital, Mahidol Univ., Mahidol University, Bangkok, Thailand; [5]Dept. of Anat., Fac. of Medicine, Chiang Mai Univ., Chiang Mai, Thailand; [6]Dept. of Anat., Fac. of Sci., Mahidol University, Bangkok, Thailand

Abstract: Glutamate has been reported to lead to neurodegenerative diseases, including Parkinson's and Alzheimer's diseases. While apoptosis plays a role in glutamate-mediated

toxicity, the related mechanism is through reactive oxygen species accumulation and excessive oxidative stress with a resultant of increased neuronal cell death. It is well known that germinated brown rice (GBR) contains high content of gamma aminobutyric acid (GABA), which exerts various pharmacological effects. However, the mechanism of neuroprotective effects of GABA in GBR is still undefined. In this study, it was aimed to investigate whether GBR prevents glutamate-induced toxicity in HT22 hippocampal neuronal cells. Pure GABA compound was used as standard control and its equivalent concentrations were calculated according to the involvement of 11.9 μg of GABA in 100 mg of GBR in previous reports. The exposure of glutamate at 4mM caused 55.4 ± 0.6 % of cell viability (MTT assay) and 50.6±1.9% of apoptotic cell death (PI and Annexin V flow cytometry). Using Western blot analysis, it was mediated through an alteration in the expression of c-Jun and its active form phosphorylated c-Jun (p-c-Jun), which are downstream products of the c-Jun N-terminal kinase (JNK) mediated apoptotic pathway. In HT22 cell line, the pre and co-treatment of 100 μg/ml of GBR or 0.125 μM of its equivalent GABA concentration significantly decreased both c-Jun and p-c-Jun expression at *p value* < 0.05. Furthermore, GBR amended glutamate-induced toxicity and reduced the number of apoptotic cells through the phosphorylation of c-Jun at amino acid residual serine 73. These ameliorated actions were also blocked significantly by bicuculline, a $GABA_A$ antagonist. In conclusion, GBR shows the protective effect against glutamate-induced toxicity in HT22 hippocampal neuronal cells. Therefore, these data imply that GABA in GBR may be a potent nutraceutical to prevent neurodegenerative diseases caused by oxidative stress and apoptosis.

Disclosures: E.M. Oo: None. **F. Padungraksart:** None. **C. Turbpaiboon:** None. **L. Khowawisetsut:** None. **P. Uawithya:** None. **V. Chaisuksunt:** None. **P. Sobhon:** None. **S. Chompoopong:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.10/F45

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: BMBF 01EO 0801
DFG EXC257 NeuroCure

Title: Inhibition of interleukin 6 signaling prevents paclitaxel-induced neuropathy in mice

Authors: *W. BOEHMERLE[1], P. HUEHNCHEN[1], M. ENDRES[2];
[1]Charite Universitaetsmedizin Berlin, Berlin, Germany; [2]Charité-Universitätsmedizin, Berlin, Germany

Abstract: Neurotoxic phenomena are among the most common side effects of cytotoxic chemotherapy and affect a large number of patients. With a prevalence of 0.5% of the general population, chemotherapy-induced peripheral neuropathy (CIN) is an immense yet unmet medical need. The microtubule-stabilizing drug paclitaxel frequently leads to CIN, which further increases the burden of disease and often necessitates treatment limitations. The pathophysiology of CIN remains poorly understood: It was previously shown that paclitaxel binds to the neuronal calcium sensor-1 (NCS-1) protein, which modulates the Inositol-1,4,5-trisphosphate receptor ($InsP_3R$) inducing calcium (Ca^{2+}) release from the endoplasmatic reticulum in dorsal root ganglia neurons (DRGN). The subsequent activation of the Ca^{2+}-dependent protease calpain contributes to cell death of DRGN *in vitro*. However, other studies point to an inflammatory reaction after paclitaxel treatment with cytokine release and macrophage infiltration of DRGN. In this study, we aimed to investigate the role of the pro-inflammatory cytokine interleukin-6 (IL-6) in the development of paclitaxel-induced neuropathy and elucidate possible upstream and downstream molecular targets of IL-6 signaling. We demonstrate that adult male IL-6 knockout mice are protected from developing functional and histological signs of paclitaxel-induced neuropathy. Our *in vitro* data shows that DRGN produce IL-6 after paclitaxel exposure, which could be prevented by co-treatment with the calpain inhibitor MDL28170. Inhibition of the NCS-1 - $InsP_3R$ interaction by co-incubation with therapeutic levels of lithium blocked IL-6 release from DRGN after paclitaxel treatment. Furthermore, a preemptive application of an IL-6-neutralizing antibody (MAB406) resulted in the prevention of paclitaxel-induced neuropathy in adult C57Bl/6 mice. Histological analysis confirmed the protective effect of MAB406 treatment prior to paclitaxel application.
In conclusion, we demonstrate that the cytokine IL-6 is essential for the development of paclitaxel-induced neuropathy in mice. Pharmacological interference of IL-6 signaling with an IL-6-neutralizing antibody prevents paclitaxel induced neuropathy. This is of clinical interest as it was previously shown that patients receiving IL-6 neutralizing antibodies reported less symptoms of CIN. Additionally, IL-6 contributes to tumor
progression in certain cancers. Thus, preventive treatment with IL-6-neutralizing antibodies might yield synergistic effects regarding an enhanced antiproliferative treatment and prevention of dose-limiting neurotoxic side effects of chemotherapy.

Disclosures: W. Boehmerle: None. **P. Huehnchen:** None. **M. Endres:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.11/F46

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Small molecule inhibitors of SARM1 prevent axonal degeneration *in vitro* and *in vivo*

Authors: *R. KRAUSS, T. BOSANAC, T. M. ENGBER, R. DEVRAJ, R. HUGHES;
Disarm Therapeutics , Cambridge, MA

Abstract: Axonal degeneration is an early and ongoing event that causes disability and disease progression in many neurodegenerative disorders of the central, peripheral, and ocular nervous systems, including multiple sclerosis, ALS, peripheral neuropathies, and glaucoma. SARM1 is the central driver of an evolutionarily conserved program of axonal degeneration downstream of inflammatory, mechanical, metabolic, or chemical insults to the axon. SARM1 contains an intrinsic NADase enzymatic activity essential for its pro-degenerative functions, making it a compelling therapeutic target to treat neurodegeneration characterized by axonopathy.
We have screened a small molecule library to identify inhibitors of SARM1 enzymatic activity using a biochemical assay. With these screening hits as a starting point, we developed potent SARM1 inhibitors that protect rodent and human axons *in vitro* from mechanical, chemical and metabolic damage. In sciatic nerve axotomy (SNA) and a paclitaxel model of chemically-induced peripheral neuropathy (CIPN), we observed that SARM1 inhibitors prevented increases in nerve cADPR, a proximal biomarker of SARM1 activity, and plasma NF-L, a clinically accessible downstream biomarker of axonal degeneration proposed for diagnostic and prognostic use in several neurodegenerative disorders.
This is the first demonstration that pharmacological inhibition of SARM1 can reproduce the axonal protective phenotype observed in SARM1 knockout mice. The availability of SARM1-dependent biomarkers of axonal degeneration enables rapid translation of SARM1 inhibitor therapeutics from discovery to the clinic. SARM1 inhibitors have the potential to prevent axonal degeneration in peripheral and central axonopathies and provide a transformational disease-modifying treatment for these disorders.

Disclosures: R. Krauss: A. Employment/Salary (full or part-time):; Disarm Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Disarm Therapeutics. **T. Bosanac:** A. Employment/Salary (full or part-time):; Disarm Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Disarm Therapeutics. **T.M. Engber:** A. Employment/Salary (full or part-time):; Disarm Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Disarm Therapeutics. **R. Devraj:** A. Employment/Salary (full or part-time):; Disarm Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Disarm Therapeutics. **R. Hughes:** A. Employment/Salary (full or part-time):; Disarm Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Disarm Therapeutics.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.12/G1

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: A GLP1 receptor agonist ameliorates disease progression in mouse models of monogenic infantile neurodegenerative diseases

Authors: *L. POUPON BEJUIT, M. P. HUGUES, S. WHALER, A. A. RAHIM;
UCL Sch. of Pharm., London, United Kingdom

Abstract: Rare infantile neurological disorders are particularly challenging to treat given the lack of sufficient knowledge of the pathology and the rapid progression of disease. These genetic disorders are usually terminal as there are currently no effective disease-modifying therapies available to treat them.
GLP1-R agonists that are approved for the treatment of type 2 diabetes mellitus have been shown to be neuroprotective in several animal models of adult neurodegeneration and could be a good therapeutic option to attempt to treat rare infantile neurological disorders. Semaglutide is a modification of existing GLP1-R agonist and this newer version have been recently develop with a longer half-life of 7 days. For the first time, we investigated the neuroprotective effects of the once-weekly GLP1-R agonist semaglutide in two unrelated mouse models of infantile genetic neurodegenerative disease; Niemann-Pick disease type C and Infantile Neuroaxonal Dystrophy, which are respectively knock-out for the gene *NPC1* and *Pla2G6*.
In this study, we demonstrate that a systemic administration of semaglutide improved locomotor function and had significant neuroprotective effects on both diseases. The molecule is also able to reduce neuroinflammation, apoptosis and microglia activation. These results are supportive of semaglutide having a potential therapeutic application as a treatment for these two unrelated NPC1 and INAD diseases but also others for which there is no treatment available.
Keywords: semaglutide, Niemann-Pick, Infantile Neuroaxonal Dystrophy, GLP1-R, neuroinflammation, apoptosis

Disclosures: L. Poupon bejuit: None. **M.P. Hugues:** None. **S. Whaler:** None. **A.A. Rahim:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.13/G2

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NCCIH 1R21AT009734

Title: High choline diet prevents cyclophosphamide- and doxorubicin-induced reductions in high affinity choline uptake in the striatum and hippocampus of C57Bl/6J and MMTV-PyVT mice and attenuates tumor growth

Authors: B. JOHNS, L. WECKER, ***R. M. PHILPOT**;
Psychiatry and Behavioral Neurosci., Univ. South Florida, Morsani Col. of Med., Tampa, FL

Abstract: Women constitute the majority of patients who report chemotherapy-related cognitive deficits, deficits of learning, memory, attention and processing speed that can impair day-to-day functioning. Many chemotherapeutic agents suppress ovarian function, decreasing circulating estrogen levels. Because estrogen regulates high affinity choline uptake (HACU) and HACU is the rate-limiting step for acetylcholine synthesis, chemotherapeutic agents may indirectly impair cholinergic systems that mediate cognitive functions. The present study determined whether cyclophosphamide (CYP) and doxorubicin (DOX) could reduce circulating estradiol (E^2) and impair HACU in the frontal cortex (CTX), striatum (STR) and hippocampus (HCC) of nontumor-bearing (C57Bl/6J) and tumor-bearing (MMTV-PyVT) female mice. Because high choline diets can maintain cholinergic function under conditions of high neuronal demand, the present study also determined whether a 2% choline diet could prevent the effects of CYP+DOX on HACU.

3 days following administration of CYP+DOX or equivalent volumes of saline: 1) circulating E^2 was 20-30% lower in nontumor- and tumor-bearing mice administered CYP+DOX (37 ±7 and 37 ±5 pg/ml, respectively) than in nontumor- and tumor-bearing control mice (54 ±11 and 46 ±17 pg/ml, respectively); 2) HACU was 8-18% lower in the STR of nontumor- and tumor-bearing mice administered CYP+DOX (167 ±11 and 155 ±8 pmol/mg/5min, respectively) than in nontumor- and tumor-bearing control mice (181 ±6 and 189 ±11 pmol/mg/5min, respectively); and 3) HACU was 11-16% lower in the HCC of nontumor- and tumor-bearing mice administered CYP+DOX (46 ±4 and 46 ±3 pmol/mg/5min, respectively) than in nontumor- and tumor-bearing control mice (55 ±4 and 52 ±2 pmol/mg/5min, respectively). HACU in the CTX was unaffected by CYP+DOX.

When nontumor- and tumor-bearing mice were placed on 2% choline two weeks prior to chemotherapy, circulating E^2 and HACU were unaffected by CYP+DOX administration. Importantly, after 1 week, the total tumor volume of mice on standard diet increased by 85%

(1513 ±180mm^3) while those on 2% choline increased by only 54% (1200 ±162mm^3). Further, after 2 weeks, mice placed on 2% choline receiving CYP+DOX exhibited total tumor volumes (1068 ±196mm^3) that were 23-35% smaller than that of mice on standard diet receiving CYP+DOX (1392 ±296mm^3) or saline (1645 ±230mm^3) and 17% smaller than mice on 2% choline receiving saline (1283 ±247mm^3). Therefore, a 2% choline diet protects against CYP+DOX-induced impairments of circulating E^2 and HACU, attenuates tumor growth and may enhance the anti-tumor effects of CYP+DOX.

Disclosures: B. Johns: None. **L. Wecker:** None. **R.M. Philpot:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.14/G3

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Erythropoietin induces neurogenesis gene expression and JAK/STAT signaling components 2h after application and reverts damage in hippocampal Ca1 cells

Authors: *S. F. CORNELIO-MARTINEZ;
Biologia Celular y Mol., Ctr. Universitario De Ciencias Biológicas Y Agro, Guadalajara, Mexico

Abstract: Background: Glutamate is the major excitatory neurotransmitter in the brain involved in physiological events. However at high extracellular concentrations it triggers excitotoxicity. Previously, we reported neuroprotection mediated by Erythropoietin (EPO) against excitotoxicity in the hippocampus of neonate rats through the induction of its own expression and EPO receptor (EPOR) (Rivera-Cervantes *et al.* 2019). This work is focused on the induction of JAK/STAT pathway and neurogenesis genes mediated by monosodium glutamate (MSG) and EPO in the hippocampus of neonate rats. Methods: Neonate rats were administered with MSG at 1, 3, 5, and 7 postnatal days (PD), and recombinant-human EPO (rhEPO) at 8 PD. Animals were killed 24h after last application of MSG and 2, 6, 12 and 24h after rhEPO treatment. Total mRNA was isolated from the hippocampus and used to synthetize cDNA. We utilized RT2 Profiler Microarrays for JAK/STAT and Neurogenesis to determined gene expression changes by Real-Time PCR. Results: GMS administration did not cause an effect on JAK/STAT pathway and related genes, while it induces an up-regulation of 9 neurogenesis genes (S100a6, Bmp8a, Cxcl1, Hes1, Dcx, Ntf3, Ascl1, Dvl3 and Ep300). Contrastingly, there was an up-regulation of genes JAK1, JAK2, STAT1 and STAT3 of the JAK/STAT pathway and up-regulation of 83 neurogenesis genes, because rhEPO treatment. Furthermore, 32 of the 83 neurogenesis genes belong to Notch, Wnt and BMP signaling pathways, which plays key roles in the in the regulation of neurogenesis. Conclusions: We observed a coordinated response of neurogenic gene expression matched by an upregulation of the JAK/STAT pathway upon rhEPO treatment.

This correlated with a major reversion of MSG-induced damage. In addition, we consider there is evidence to support that abnormal neural morphology caused by MSG excitotoxicity is owed to the expression of a number of neurogenesis genes.

Disclosures: S.F. Cornelio-Martinez: None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.15/G4

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: 6R43CA199928-02

Title: NYX-2925, a novel NMDA receptor modulator, improves chronic pain and its affective state in rats with paclitaxel-induced neuropathy

Authors: *N. GHOREISHI-HAACK, J. S. BURGDORF, J. M. PRIEBE, J. D. AGUADO, A. M. LYNCH, M. BOWERS, C. N. CEARLEY, J. R. MOSKAL;
Aptinyx Inc., Evanston, IL

Abstract: NYX-2925 is a novel, oral, small molecule NMDA receptor modulator currently in clinical development for the treatment of chronic pain including painful diabetic peripheral neuropathy (DPN) and fibromyalgia. Results from previous studies demonstrated the analgesic effects of NYX-2925 in rat models of nerve injury-induced neuropathic pain, DPN, and formalin-induced persistent pain. In the studies presented here, the effects of NYX-2925 were evaluated in a rat model of chemotherapy-induced peripheral neuropathy (CIPN) using measures of both evoked and non-evoked pain. To induce CIPN, rats were given 4 injections of paclitaxel (2 mg/kg, i.p.) every other day. The onset of neuropathy was evaluated weekly, and only rats with baseline allodynia were included in the studies. To measure mechanical hypersensitivity, a single dose of NYX-2925 (1-100 mg/kg, p.o.) was administered to CIPN rats 3 weeks after the first paclitaxel injection. Tactile allodynia was evaluated at 1 hour, 24 hours, and 1 week after NYX-2925 administration. NYX-2925 at 10 mg/kg (at the 1h and 24h timepoints) and 30 mg/kg (at the 24h time point) alleviated tactile allodynia. For thermal hypersensitivity measures, NYX-2925 was administered orally and cold allodynia evaluated via the acetone test 1 hour after drug administration. A single dose of NYX-2925 (10 mg/kg, p.o.) resulted in significant thermal analgesia when compared to vehicle-treated rats. To evaluate negative affective components linked with chronic pain, NYX-2925 (10 mg/kg, p.o.) was administered to CIPN rats, and spontaneous ultrasonic vocalizations (USVs) measured in the homecage recording for 24 hours. CIPN rats showed higher rates of spontaneous aversive calls (20 kHz USVs), and decreased rates of spontaneous hedonic calls (50 kHz USVs). NYX-2925 decreased the number of aversive calls

and increased the number of hedonic calls emitted by CIPN rats. Non-evoked pain was also measured by the frequency and type of USVs emitted during the non-tactile stimulation periods of a heterospecific rough-and-tumble play assay 1 hour after NYX-2925 (10 mg/kg, p.o.) administration. In the heterospecific rough-and-tumble play assay, NYX-2925 administration increased the number of hedonic calls during the non-stimulation periods that were suppressed by CIPN in vehicle-treated rats. Together, these data suggest that NYX-2925 alleviates evoked pain, both mechanical and thermal hypersensitivity, induced by paclitaxel treatment. Furthermore, these data suggest that NYX-2925 improves negative affect induced by CIPN in the rat.

Disclosures: **N. Ghoreishi-Haack:** None. **J.S. Burgdorf:** None. **J.M. Priebe:** None. **J.D. Aguado:** None. **A.M. Lynch:** None. **M. Bowers:** None. **C.N. Cearley:** None. **J.R. Moskal:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.16/G5

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NMRC Translational Clinical Research (TCR) Flagship Award - NMRC/TCR/013-NNI/2014

Title: Pharmacological enhancement of integrated stress response ameliorates the proteotoxicity-mediated neuropathologies

Authors: *J. RAJAMEENAKSHI SUNDARAM[1], Y. WU[2], I. C. LEE[3], S. E. GEORGE[2], P. HO[1], M. TIO[1], S. SHENOLIKAR[2], E.-K. TAN[1];
[1]Natl. Neurosci. Inst., Singapore, Singapore; [2]Cardiovasc. & Metabolic Disorders, [3]MD Dept., Duke-NUS Med. Sch., Singapore, Singapore

Abstract: Defects in protein quality control systems lead to accumulation and aggregation of misfolded proteins, hallmarks of many neurodegenerative diseases. Further perturbations activate series of parallel adaptive responses to reestablish protein homeostasis. Pharmacological modulation of the integrated stress response (ISR), mediated by eukaryotic translation initiation factor 2α (eIF2α) phosphorylation-dephosphorylation and downstream signaling shows great promise in cytoprotection in many neurodegenerative diseases. Guanabenz (GBZ), an α-adrenergic receptor agonist, crosses the blood-brain barrier to restore protein homeostasis and attenuates neurotoxicity in several cellular and animal models of neurodegenerative disease. This current study pursued an analogueing strategy to identify novel compounds with improved ability to modulate ISR and to reduce the cellular burden of misfolded proteins with the ultimate

goal of providing greater cytoprotection than Guanabenz. We analyzed 432 structurally distinct GBZ analogues for activation of ISR signaling and identified PromISR-6, a potent GBZ analogue that selectively activated PERK (Protein Kinase R-like ER kinase)-eIF2α signaling pathway. The sustained eIF2α phosphorylation, translational repression and autophagy induction effects make PromISR-6, the most efficacious GBZ analogue in reducing Huntingtin aggregation and promoting survival in a PC12 model (Inducibly expressing mutant Huntingtin, GFP-mHtt-74Q) of Huntington's disease. Subsequently, we explored the effects of PromISR-6 on Parkinson's disease (PD) using a *Drosophila* model that express mutant α-Synuclein A30P protein. The α-Synuclein A30P expression-mediated behavioral and neuropathological deficits such as locomotor dysfunction, loss of dopaminergic neurons and reduced life-span were investigated in flies treated with PromISR-6 from day one post-occlusion up to 40 days. Our data describe a novel GBZ analogue and its spectrum of biological activities that lays the foundation for future development of efficacious GBZ-based therapeutics to treat neurodegenerative diseases.

Disclosures: J. Rajameenakshi Sundaram: None. **Y. Wu:** None. **I.C. Lee:** None. **S.E. George:** None. **P. Ho:** None. **M. Tio:** None. **S. Shenolikar:** None. **E. Tan:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

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Program #/Poster #: 476.17/G6

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Can maraviroc, the antiretroviral agent used to treat HIV, block the development of opioid addiction? Evidence from multimodal MRI and behavioral testing in rats

Authors: *S. IRIAH[1], C. BORGES[3], U. SHALEV[3], X. CAI[2], D. MADULARU[4], P. P. KULKARNI[5], C. F. FERRIS[6];
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Abstract: Maraviroc (MVC) is an antiretroviral agent and C-C chemokine (CCR5)-receptor agonist that is currently used for the treatment HIV. The interaction between chemokine and opioid receptor signaling, suggests that MVC could be a possible mode of treatment therapy for opioid addiction. Opioids like oxycodone (OXY), are used as analgesics to alleviate pain, and repeated exposure can lead to the development of tolerance and addiction. The present study consisted of two experimental groups of rats, one exposed to daily IP injections of MVC (10 mg/kg, n = 8) and the other to saline vehicle (n = 9) one hr before placing them into a testing

chamber consisting of two adjoining rooms previously identified as preferable or non-preferable. On this first day of testing all rats were given an IP injection of OXY (3.0 mg/kg) and placed into their non-preferred room and filmed for 15 min before removal. On day 2 all rats are injected with saline immediately before being placed into their preferred room. This treatment and placement procedure were done for 8 consecutive days so that each rat was exposed to OXY four times in their non-preferred room and saline in their preferred room. On day 9 they were exposed to the open chamber and scored for the time spent in either room. MVC significantly decreased place preference as compared to vehicle suggesting it interfered with the development of drug seeking behavior following repeated exposure to OXY. In contrast, acute treatment with MVC (10 mg/kg, IP) had no significant effect on established OXY self-administration (0.1 mg/kg/infusion; IV) under a fixed-ratio or progressive-ratio schedule of reinforcement. The apparent diffusion coefficient derived from diffusion weighted imaging, a measure of parenchymal edema, was significantly altered in hippocampus and anterior cerebellum in vehicle treated rats but not with MVC treatment. Similarly, resting state BOLD MRI showed enhanced functional coupling with the accumbens/ventral pallidum with vehicle but not MVC. These data suggest the OXY-induced changes in gray matter microarchitecture and functional connectivity were blocked by the pretreatment with MVC.

Disclosures: S. Iriah: None. **C. Borges:** None. **U. Shalev:** None. **X. Cai:** None. **D. Madularu:** None. **P.P. Kulkarni:** None. **C.F. Ferris:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.18/G7

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Development of a human high throughput screening platform for simultaneous assessment of compound efficacy and safety for glioblastoma treatment

Authors: R. PADILLA, A. FANTON, C. ANDERSEN, O. GUICHERIT, C. CARROMEU, ***F. ZANELLA**;
StemoniX, San Diego, CA

Abstract: Glioblastoma Multiforme (GBM) are aggressive brain tumors with poor prognosis. Therapeutic management for GBM is currently limited; with Temozolomide currently being the standard of treatment for GBM. However, even when combined with radiotherapy only up to 20 percent of patients show favorable response to Temozolomide. Importantly, due to their requirements for potency and efficacy, oncology drugs can be quite toxic. In this study, the U87 GBM cell line was tagged with mCherry to serve as a traceable model for GBM. To study their growth behavior in a physiologically relevant system amenable to drug discovery, U87-mCherry

cells were co-cultured with human induced pluripotent stem cell-derived cortical neurospheroids in a high throughput based screening platform. The neurospheroids are composed of a balanced co-culture of cortical neurons and astrocytes with mature functional neuronal circuitry evidenced by spontaneous calcium oscillations. Previously, the model has been successfully utilized in independent neurotoxicity and drug discovery studies. Thus, by combining U87-mCherry and the high throughput neurospheroids, the proliferation and infiltration patterns of the GBM cells as well as the preservation of cortical functionality can be analyzed within the same high throughput platform. Proof-of-principle studies focused on Temozolomide, Carmustin, Paclitaxel and Cisplatin to identify and profile compound efficacy versus it's toxicity with the ultimate goal of providing a platform that can separate safe and effective compounds from those that have minimal efficacy and deleterious toxicity. In summary, the work described herein suggests a novel framework approach for combining human induced pluripotent stem cell-derived cortical neurospheres with GBM, enabling more streamlined drug discovery of compounds against aggressive brain cancers.

Disclosures: **R. Padilla:** A. Employment/Salary (full or part-time):; StemoniX. **A. Fanton:** A. Employment/Salary (full or part-time):; StemoniX. **C. Andersen:** A. Employment/Salary (full or part-time):; StemoniX. **O. Guicherit:** A. Employment/Salary (full or part-time):; StemoniX. **C. Carromeu:** A. Employment/Salary (full or part-time):; StemoniX. **F. Zanella:** A. Employment/Salary (full or part-time):; StemoniX.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.19/G8

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Gintonin, a ginseng-derived exogenous lysophosphatidic acid receptor ligand, attenuates mutant Huntingtin toxicity

Authors: *B. CHEON[1], M. JANG[1], Y. CHANG[1], S. LEE[2], J. CHOI[1], I.-H. CHO[1];
[1]Kyung Hee Univ., Seoul, Korea, Republic of; [2]Korea Inst. of Sci. and Technol. (KIST), Seoul, Korea, Republic of

Abstract: Gintonin is a ginseng-derived exogenous G protein-coupled lysophosphatidic acid (LPA) receptor ligand. Although previous *in vitro* and *in vivo* studies demonstrated the therapeutic role of gintonin against Alzheimer's and Parkinson's diseases, the neuroprotective effects of gintonin in Huntington's disease (HD) are still unknown. In this study, we investigated whether gintonin could ameliorate the mutant huntingtin toxicity in cellular or animal model of HD. Gintonin reduced cell death and mutant huntingtin (*HTT*) aggregates in ST*Hdh* cells. It also mitigated neurological impairment in mice with adeno-associated viral (AAV) vector serotype

DJ-mediated overexpression of N171-82Q-mutant *HTT* in the striatum. Taken together, our findings firstly suggested that gintonin exerts neuroprotective effects in ST*Hdh* cells and AAV vector-infected model of HD. Thus gintonin might be a therapeutic candidate to treat HD.

Disclosures: B. Cheon: None. **M. Jang:** None. **Y. Chang:** None. **S. Lee:** None. **J. Choi:** None. **I. Cho:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.20/G9

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NHMRC
International Research Training Program Scholarship

Title: At the forefront of mitochondrial dysregulation: Deoxygedunin imparts neuroprotection via mitophagy in retinal cells

Authors: *A. MANGANI[1], C. JOSEPH[1], M. MIRZAEI[1], V. GUPTA[2], S. GRAHAM[2]; [2]FMHS, Clin. Med., [1]Macquarie Univ., Sydney, Australia

Abstract: Mitophagy is a quality control mechanism to mitigate dysfunctional and fissioned mitochondria through a catabolic degradation process akin to autophagy. There are only a few studies that link anomalous mitochondrial autophagy or mitophagy to ocular dysfunction. A natural compound, which is also a TrkB agonist deoxygedunin has shown potent neurotrophic activity. Herein, we examine the effect of deoxygedunin on mouse photoreceptor cells and mice retinas and evaluate if mitophagy acts as an underlying process in administering neuroprotection. Mouse photoreceptor cell line 661W ($3x10^5$) were subjected to pharmacological inhibitors, Cyclotraxin-B (CTX-B,1uM): TrkB inhibitor, TAT PEP-5 (TAT, 1uM):p75NTR inhibitor and Deoxygedunin(1uM). To accurately, assess alterations in mitochondrial regulation, we incubated 661W cells and fresh ex-vivo mice retinas with Rotenone (400nM) in culture media. Mitophagy markers were assessed by western blotting of sample lysates and immunocytochemistry using specific antibodies (n=3).

In our studies, deoxygedunin treatment alone resulted in increased phosphorylation of Ulk1 S757. Inhibition of TrkB receptor via CTX-B, displayed, significant downregulation of pUlk1 S757 compared to p75NTR receptor inhibition via TAT. Further treatment of deoxygedunin, rescued the phosphorylation of Ulk1 S757 in 661W cells and mice retinas treated with inhibitors. Deoxygedunin also upregulated mitophagy markers downstream to Ulk1, such as BNIP3, BNIP3L/Nix but did not induce apoptosis. Downregulation of PINK1 was markedly seen in CTX-B than TAT treated cells and retinal tissues, deoxygedunin treatment resulted in the

elevation of these proteins leading to phosphorylation of Ubiquitin at S65 thereby activating Parkin. Distinct cargo receptors such as SQSTM1/p62, Optineurin, and NDP52 were also activated upon ubiquitination (pUb S65) upon deoxygedunin treatment. Finally, LC3B which aids in recruiting the autophagosome to lysosome, were highly expressed in deoxygedunin treated retinal cells and tissues, resulting in targeting of dysfunctional mitochondria to lysosomes resulting in mitophagy. Similar results were obtained with rotenone-treated cells but albeit to a lesser extent in ex-vivo retina.
Overall these results suggest that deoxygedunin treatment rescues retinal cells and tissues undergoing apoptosis upon mitochondrial dysregulation by activating the mitophagy cascade. This study also highlights the potential of deoxygedunin as a pharmacological drug in mitigating retinal diseases and opens up possible avenues in treating other neurodegenerative diseases.

Disclosures: A. Mangani: None. **C. Joseph:** None. **M. Mirzaei:** None. **V. Gupta:** None. **S. Graham:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.21/G10

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DA035714
DA041932

Title: Systemic administration of a novel allosteric modulator, SRI-32743, alleviates HIV-1 Tat protein-potentiated cocaine rewarding effects in HIV-1 Tat transgenic mice

Authors: *J. ZHU[1], P. M. QUIZON[2], Y. Y. WANG[2], H. M. STACY[3], S. O. CIRINO[3], J. P. MCLAUGHLIN[4], S. ANANTHAN[5];
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Abstract: Cocaine abuse has been shown to increase the incidence of HIV-1 associated neurocognitive disorders (HAND). We have demonstrated that HIV-1 Tat protein allosterically modulates dopamine (DA) reuptake via human DA transporter (hDAT). This study determined whether a novel allosteric modulator, SRI-32743, pharmacologically blocks Tat binding to hDAT and alleviates Tat-potentiated cocaine rewarding effects in inducible HIV-1 Tat transgenic (iTat-tg) mice. The iTat-tg mouse model recapitulates many aspects of neurocognitive impairments observed in HIV infected individuals. SRI-32743 inhibited [^{3}H]DA uptake (IC_{50},

9.9 µM) with a 17-fold greater inhibition than the potency of [^{3}H]WIN35,428 binding (IC_{50}, 168 µM) with 68.4% and 71.4% of its E_{max}, respectively. Tat (140 nM) induced 30% and 20% reductions in [^{3}H]DA uptake and [^{3}H]WIN35,428 binding, respectively, which were attenuated by SRI-32743, while SRI-32743 alone did not alter DAT function and binding. SRI-32743 and indatraline, a competitive DAT inhibitor, increased the cocaine IC_{50} values of [^{3}H]DA uptake by 164% and 280%, respectively. The cocaine (1 µM)-induced dissociation rate (0.238 ± 0.030) of [^{3}H]WIN35,428 binding was similar to that induced by 50 nM SRI-32743 (0.187 ± 0.027); however, SRI-32743 slowed the cocaine-induced dissociation rate to 0.032 ± 0.005. Pharmacokinetics study shows that SRI-32743 is BBB-permeable with a 2.52 and 2.08 ratio of brain to plasma concentration (ng/ml) at 15 and 60 min, respectively. Following a 14 day-doxycycline treatment to induce Tat protein, the iTat-tg mice exhibit a 2-fold potentiation of cocaine-CPP which was dose-dependently ameliorated by pretreatment of SRI-32743 (1 or 10 mg/kg/d, i.p.) prior to CPP, while SRI-32743 alone did not alter basal cocaine-CPP relative to saline controls. These preliminary data raise the exciting possibility of potential therapeutic interventions for neurocognitive dysfunction in HAND, particularly effective for those with concurrent cocaine abuse.
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Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.22/G11

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: MU Research Council

Title: Effects of dietary DHA on lipid peroxidation products in the brain and other body organs

Authors: *G. Y. SUN[1], **M. K. APPENTENG**[2], B. YANG[7], R. LI[3], T. WOO[4], B. M. KILLE[5], K. L. FRITSCHE[6], J. CUI[8], Z. GU[9], M. J. WILL[10], D. Q. BEVERSDORF[11], C. M. GREENLIEF[12]; [1]Biochem., Univ. Missouri, Columbia, MO; [2]Chem., [3]Anat. and Pathology, [4]Neurosci., [5]Psychological Sci., [6]Nutr. and Exercise Physiol., Univ. of Missouri, Columbia, MO; [7]Chem., Univ. of Missouri-Columbia, Columbia, MO; [8]Path & Ana Sci. Dept., U of Missouri-Columbia Sch. of Med., Columbia, MO; [9]Pathol & Anat Sci., Univ. of Missouri Columbia Sch. of Med., Columbia, MO; [10]Dept Psychology, Univ. of Missouri Columbia Dept. of Psychological Sci., Columbia, MO; [11]Dept Radiol, Neurol, Psychol Sci, DGS of INP, [12]Univ. of Missouri Columbia, Columbia, MO

Abstract: Phospholipids in brain cell membranes are enriched in docosahexaenoic acid (DHA). Besides its role in modulating membrane fluidity, this (n-3) polyunsaturated fatty acid (PUFA) is known to offer diverse functions, in particular, synthesis of oxylipins that are pro-resolving. DHA is important in the developing brain. In recent years, (n-3)PUFAs, in the form of fish oil, have been widely used and are one of the most consumed supplements in human populations. Besides DHA, brain phospholipids also show high levels of arachidonic acid (ARA), an (n-6)PUFA which is linked to inflammatory responses. The apparent Yin-Yang mechanism for DHA and ARA is due mainly to different phospholipases A2 (PLA2) for their release from membrane phospholipids. Both PUFAs are susceptible to lipid peroxidation by free oxygen radicals, leading to production of 4-hydoxyhexenal (4-HHE) and 4-hydroxynonenal (4-HNE), respectively. These lipid-derived aldehydes are present in all brain regions as well as in body organs. Considering the involvement of cytosolic PLA2 and that the release of ARA is associated with neuro-inflammation, neurotrauma and neurodegenerative diseases, it is reasonable to extend efforts to understand factors that modulate the (n-3)/(n-6) PUFA ratio and their peroxidation products. In our recent study, weanling pups from dams given control and DHA (1%) diets showed changes in the (n-3)/(n-6) PUFA ratio in all brain regions. However, increases in 4-HHE (but not 4-HNE) were observed only in the cerebral cortex and hippocampus. In the present study, we measured the concentration of 4-HHE and 4-HNE in a group of adult mice fed a DHA (1%) diet for three weeks. Results demonstrated minimal changes in the brain but substantial increases in 4-HHE levels (but not 4-HNE) in the heart. Feeding DHA to adult mice for three weeks also increased 4-HHE levels in liver but not in kidney. Although the physiological significance of changes in fatty acids and peroxidation products upon DHA supplementation needs to be examined further, these studies provide evidence of different extents of lipid peroxidation in different organs and with respect to different ages in mice.

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Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.23/G12

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Duke Department of Psychology and Neuroscience
NIH R21 AG055877-01A1 to NT

Title: Mitigating postoperative neuroinflammation with presurgical choline-supplemented diet in male mice

Authors: *S. V. MAURER[1], C. KONG[2], N. TERRANDO[2], C. L. WILLIAMS[1];
[1]Dept. of Psychology and Neurosci., [2]Anesthesiol., Duke Univ., Durham, NC

Abstract: Perioperative neurocognitive disorders (PND) occur when peripheral surgery leads to cognitive deficits, partly due to neuroinflammation (Subramaniyan & Terrando, 2019). Previous research has shown that increased neuroinflammation and corresponding cognitive deficits in a contextual fear response task due to peripheral surgery is prevented by cholinergic receptor agonists (Terrando et al., 2011). Hence, we sought to assess the impact of dietary choline in preventing the neuroinflammation after peripheral surgery. Nine-week old male C57/BL6J mice were given either a synthetic control diet (1.1 g/kg choline) or a choline-supplemented diet (4.95 g/kg choline) *ad libitum* for 3 weeks. Mice were then either given tibial fracture surgery, or a sham surgery. Mice were sacrificed and brains were fixed in 4% paraformaldehyde. Brains were sliced and stained using immunohistochemistry (IHC) for ionized calcium-binding adapter molecule 1, a marker for microglia. Microglia in the dentate gyrus of the hippocampus were counted and classified based on activation state. The numbers of activated microglia were increased in the Surgery+Control Diet group, but this effect was blunted in the Surgery+Choline Diet group. No increase or decrease was seen in the sham surgery groups. Based on these results, we next examined the effects of choline diet and peripheral surgery on cell division in the hippocampus. Mice of the same age and sex were given the same dietary groups for 3 weeks. They were then given either tibial fracture surgery or no surgery. 5-bromo-2'-deoxyuridine (BrdU) injections were administered to analyze cell division 1 hour and 10 hours post-surgery. Mice were sacrificed either 24 hours or 2 weeks after surgery. Brains were extracted, fixed, sliced and stained using IHC to stain for BrdU, doublecortin (DCX), and glial fibrillary acidic protein (GFAP) for dividing cells, young neurons, and astrocytes, respectively. Surgery increased the numbers of BrdU+ cells at both timepoints. Though no differences in DCX expression were seen after 24 hours, an upregulation of DCX+ cells was seen in the dentate gyrus 2 weeks after peripheral surgery. Surgery also led to increased numbers of ectopic granule cells: DCX+ cells in the hilus, rather than in the granule cell layer of the dentate gyrus. Additionally, there was an increase in astrocytic density due to surgery, which was blunted by dietary choline supplementation prior to surgery. Overall, our data indicate that presurgical dietary choline can resolve surgery-induced neuroinflammation and may serve as a novel treatment for perioperative neurocognitive disorders.

Disclosures: S.V. Maurer: None. **C. Kong:** None. **N. Terrando:** None. **C.L. Williams:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.24/G13

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NSF 1655494

Title: Naked mole-rats, neuroprotection, and the endocannabinoid system: Upregulation of cannabinoid receptor 1 in naked mole-rats leads to increased control of neuroprotective characteristics during hypoxic and anoxic insult

Authors: *B. M. BROWE[1], T. J. PARK[2], J. R. LARSON[3];
[1]Depart of Biol. Sci., [2]Dept of Biol. Sci., Univ. of Illinois at Chicago, Chicago, IL; [3]Dept Psychiatry, Univ. of Illinois at Chicago Dept. of Psychiatry, Chicago, IL

Abstract: Naked mole-rats (NMRs) are strictly subterranean rodents that live in large communal colonies in sealed and chronically oxygen-depleted burrows. NMRs exhibit unusual tolerance to hypoxia, compared to other mammals; this tolerance involves down-regulating oxygen demand in response to low oxygen conditions. Mammalian brains typically suffer irreversible damage after brief periods of oxygen deprivation such as occur during stroke or cardiac arrest; this damage is thought to result from glutamate excitotoxicity, neuroinflammation, and oxidative stress. Brain slices from NMRs maintain synaptic transmission under anoxia and longer latency to anoxic depolarization compared to other rodents. Additionally, adult NMR brains retain the NMDA receptor subunit (GluN2D) associated with neonatal hypoxia tolerance and show a blunted intracellular calcium response to hypoxia. Retrograde synaptic signaling by endogenous cannabinoids is a form of neuromodulation in various brain regions, including the hippocampus. The endocannabinoid system has been described as an endogenous neuroprotective system that, once activated, can prevent glutamate excitotoxicity and intracellular calcium accumulation. Currently the mechanisms of cannabinoid-modulated neuroprotection during hypoxia are not well understood; however, cannabinoid agonists appear to enable robust protection from oxygen deprivation and ischemia. Also, NMDA-elicited increases in intracellular calcium are enhanced by CB1 receptor (CB1r) antagonists and inhibited by CB1r agonists. In the present study, we used hippocampal brain slices to measure electrophysiological responses to hypoxia in CA1 pyramidal neurons. Interestingly, pretreatment of NMRs with either a CB1r antagonist (AM251) or a CB1 agonist (WIN 55,212-2) maintained synaptic transmission and increased latency to anoxic depolarization after oxygen deprivation *in vitro*. We also demonstrated that CB1r appears to be highly expressed at both GABAergic and glutamatergic synapses in the hippocampus. Furthermore, analysis of multiple brain regions suggest that the NMR endocannabinoid system responds to hypoxic insult differently than other rodents as demonstrated by differential

expression levels of the endocannabinoid 2-AG after 5-hour hypoxia exposure *in vivo*. Our results indicate that the neuroprotective characteristics of the endocannabinoid system may be utilized in the hypoxia-tolerant NMR in a more direct manner than previously seen in other mammals.

Disclosures: B.M. Browe: None. **T.J. Park:** None. **J.R. Larson:** None.

Poster

476. Neuroprotective Mechanisms

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 476.25/G14

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Epigenetic regulation of microglial function during neurodegeneration

Authors: *J. SULLIVAN[1], P. AYATA[1], S. VEUGELEN[1], S. AGRAWAL[1], A. BADIMON[2], A. SCHAEFER[1];
[1]Icahn Sch. of Med. At Mount Sinai, New York, NY; [2]Neurosci., Mount Sinai, New York, NY

Abstract: As postmitotic cells, neurons are incapable of replacing themselves and, while adult neurogenesis may occur, this limited capacity cannot compensate for large-scale neuronal loss during neurodegeneration. Therefore in order to preserve brain function, it is of the utmost importance to understand the mechanisms that cause neuronal death and dysfunction. Recent work has identified a potential causal role for microglia, the brain's immune cells, in neurodegenerative diseases such as Alzheimer's disease. During homeostasis, microglia exist in diverse functional states that reflect their microenvironment and our previous work identified that the region-specific activation states of microglia is controlled by an epigenetic mechanism. However, microglia can also completely shift their morphology, transcriptome and function to enter a pro-inflammatory state after brain injury or infection. This inflammatory activity which may initially be beneficial for host defense can have extremely deleterious effects on tissue health if left unchecked. Therefore we sought to understand how transcriptional regulation impacts the inflammatory activation of microglia and if modulation of microglial functional states can impact disease progression. By targeting various epigenetic processes, we reveal different activation states of microglia to either repress inflammation or increase phagocytosis. Here we will show our most recent data highlighting the dependence of microglial function on epigenetic regulation of transcription and its potential implications for the treatment of neurodegenerative diseases.

Disclosures: J. Sullivan: None. **P. Ayata:** None. **S. Veugelen:** None. **S. Agrawal:** None. **A. Badimon:** None. **A. Schaefer:** None.

Poster

476. Neuroprotective Mechanisms

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Program #/Poster #: 476.26/G15

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH R01 NS088192
NIH R21 NS107897
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Dr. Ralph and Marian Falk Medical Research Trust-Catalyst Award
Harrington Rare Disease Scholar Award

Title: Identification of mitochondrial enhancer as therapeutic option for Huntington's disease

Authors: *D. HU[1], M. THOMPSON[2], D. ADAMS[3], X. QI[1];
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Abstract: The molecular mechanisms by which expanded huntingtin protein (Htt) leads to neuropathology in Huntington's disease (HD) have been intensively studied for decades. However, there is no treatment available for HD. We previously reported that treatment of the rationally designed peptide inhibitors sufficiently reduced the neuropathology and motor deficits in HD animal models. These findings suggest that enhancing mitochondrial function is a potential therapeutic strategy for HD. Given the challenges of clinical translation of peptide therapeutics, we tend to identify small molecule that can rescue mitochondrial function and reduce neuronal loss in HD. Screened from a pool of 3,000 bioactive molecules, CHIR99021 was the top small molecule that improved mitochondrial membrane potential, mitochondrial respiratory capacity and cell viability in HD cells. The protective effects of CHIR99201 on mitochondrial function and cell viability was validated in neurons differentiated from iPSC of HD patients. Administration of CHIR99021 efficiently prevented the loss of medium spiny neurons and the accumulation of mutant Htt aggregation, and reduced the motor deficits in both R6/2 and YAC128 HD mouse models. Treatment of CHIR99021 restrained Drp1-dependent mitochondrial fragmentation. In combination of unbiased proteomics and biochemical analyses, we further showed that treatment with CHIR99021 influenced calpastatin-calpain pathway in vitro and in vivo. Thus, our study presents a distinguished approach for drug development by targeting mitochondrial integrity, and it suggests CHIR99201 and its analogs as a potential disease-modifying treatment for HD.

Disclosures: **D. Hu:** None. **M. Thompson:** None. **D. Adams:** None. **X. Qi:** None.

Poster

476. Neuroprotective Mechanisms

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Program #/Poster #: 476.27/G16

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: K99EY029360
K99EY028625
WingsForLife Research Foundation

Title: Single-cell transcriptomic characterization of neurons with selective resilience to axonal injury reveals targets for neuroprotection

Authors: *N. M. TRAN[1], A. JACOBI[5], K. SHEKHAR[7], I. E. WHITNEY[2], I. BENHAR[7], G. HONG[8], W. YAN[3], C. WANG[9], M. E. ARNOLD[6], C. M. LIEBER[4], A. REGEV[7], Z. HE[10], J. R. SANES[1];
[2]Mol. and Cell. Biol., [3]FAS, [4]Dept. of Chem. and Chem. Biol., [1]Harvard Univ., Cambridge, MA; [5]Kirby Ctr. for Neurol., [6]Boston Children's Hospital, Harvard Med. Sch., Boston, MA; [7]Broad Inst. of MIT and Harvard, Cambridge, MA; [8]Stanford Univ., Stanford, CA; [9]Neurol., Boston Children's Hosp., Boston, MA; [10]Children's Hosp Boston, Boston, MA

Abstract: Selective neuronal vulnerability is an increasingly appreciated feature of neurodegenerative disorders. A striking example is the type-dependent degeneration of retinal ganglion cells (RGCs) following optic nerve crush (ONC): >80% of all mouse RGCs die within two weeks, but types vary dramatically in their vulnerability (X. Duan et al., Neuron, 2015). To investigate mechanisms of selective RGC resilience, we used single-cell RNA-sequencing (scRNA-seq) to track the survival and gene expression of RGC types. As a foundation, we first derived a comprehensive scRNA-seq atlas comprising 45 retinal ganglion cell (RGC) types in adult mouse and used immunohistochemistry to match molecular signatures with morphological types. We then performed scRNA-seq at six time points spanning the first two weeks after injury. We developed a novel computational framework that enabled the accurate tracking of individual RGC types after ONC, allowing us to determine the relative resilience and the kinetics of cell death for each type. Next, we utilized these rankings to examine the morphological, physiological and molecular changes in types with different resilience to ONC. We found that most vulnerable RGCs maintained dendritic morphology, firing rate, and feature selectivity for 2-5 days before declining sharply and dying, whereas resilient RGCs were robust throughout the time course. Differential expression analysis among types revealed factors correlating with resilience and susceptibility. To determine if these factors could mediate RGC survival, we used AAV-based overexpression or knockdown *in vivo* and identified several genes that improved survival. Our study presents a comprehensive and systematic framework to study selective

neuron resilience at the single cell level and identifies novel molecular targets for neuroprotection. A companion poster (A. Jacobi, N. Tran et al.) demonstrates that some of these genes also regulate axonal regeneration following injury. (Supported by NIH and Wings for Life.)

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Poster

476. Neuroprotective Mechanisms

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

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Title: Single-cell transcriptomics identify intrinsic resilience of neuronal subtypes and distinguishes specific mediators for axon regeneration after injury

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Abstract: After optic nerve crush (ONC), only ~20% of retinal ganglion cells (RGCs) survive for longer than 2 weeks and hardly any of the survivor's regenerate axons. Some axons can be induced to regenerate, however, by manipulations such as mTOR activation, but no treatments to date are sufficient to restore useful vision, and regeneration, like survival, varies dramatically among RGC types (Duan et al., Neuron, 2015). In a companion poster (Tran NM, Jacobi A et al.), we report on the use of high throughput single cell RNAseq to generate a cell atlas comprising 45 RGC types and to characterize the relative resilience to ONC across all RGC types. To identify mediators of axon regeneration, we examined gene expression differences between resilient and susceptible types at 6 times after ONC and tested the effects of differentially expressed genes on survival by AAV-based overexpression or knockdown. Here, we extended this work to seek factors that promoted axon regeneration and found some that did. They include genes that also affected survival and others that promoted regeneration but not survival. In parallel, we used similar methods to investigate the enhanced recovery observed with manipulations known to promote regeneration such as deletion of PTEN or PTEN plus SOCS3

(Sun et al., Nature 2011). These transcriptomic comparisons allowed us to identify RGC types whose survival and regeneration is improved by these treatments, as well as gene expression patterns that correlate with improved survival and regeneration. Finally, to distinguish RGCs that regenerate from those that survive but do not regenerate, we established a new retrograde labeling technique that allowed us to isolate and transcriptomically profile only regenerating RGCs. Ongoing work is aimed at determining which RGC types, among all survivors, regenerate, and identifying genes that promote regeneration.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.01/G18

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Effects of nuclear receptor reverb on proinflammatory responses in cultured microglia

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Abstract: Microglia are one of glial cells that reside in the central neuron system (CNS) and known to maintain CNS homeostasis as an immune cell. They also play a crucial role in eliciting an inflammatory response in the CNS through the production of inflammatory cytokines and are involved in the pathogenesis of various neurological diseases associated with chronic inflammation. The nuclear REV-ERB is known to exert as a transcriptional regulatory factor and involved in the regulation of circadian rhythm, inflammation, and lipid metabolism. However, the role of REV-ERB in microglial inflammatory responses is unknown. The current study investigated the effect of REV-ERB agonist SR9009 on the inflammatory response in cultured rat primary microglia. Treatment of cultured microglia with lipopolysaccharide (LPS) evoked up-regulation of inflammatory cytokines mRNA (interleukin-1β, interleukin-6, tumor necrosis factor-α). Pre-treatment with SR9009 suppressed LPS-induced inflammatory cytokines mRNA expression. Mitogen-activated protein kinase (MAPK) p38 and nuclear factor kappa B (NF-κB) are crucial in the LPS-induced pro-inflammatory cytokine expression. Stimulation of cultured microglia with LPS induced phosphorylation of both p38 and NF-κB subunit p65. These effects were significantly prevented by pretreatment with SR9009. In conclusion, these results indicate that REV-ERB is involved in the inhibition of inflammatory responses through the regulation of

pro-inflammatory cytokine expression, and the inhibitory effects of REV-ERB are mediated by blockade of MAPK p38 and NF-κB subunit p65.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: DFG grant WE 6170/1-1 (SW)
NIH/NIMH RO1MH113743 (DS)
NIH/NIMH R00MH102351 (DS)
NINDS Intramural Research Program (DSR)
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation (DS, DSR, BP)

Title: Targeted complement inhibition at synapses prevents microglia-mediated synapse elimination in demyelinating disease

Authors: *S. WERNEBURG[1], J. JUNG[1], C. M. WILLIS[3], R. B. KUNJAMMA[4], S.-K. HA[5], N. J. LUCIANO[5], G. GAO[2], S. J. CROCKER[3], B. POPKO[4], D. S. REICH[5], D. P. SCHAFER[1]; [1]Dept. of Neurobio., [2]Horae Gene Therapy Ctr., Univ. of Massachusetts Med. Sch., Worcester, MA; [3]Dept. of Neurosci., Univ. of Connecticut Sch. of Med., Farmington, CT; [4]Univ. of Chicago, Chicago, IL; [5]Natl. Inst. of Neurolog. Disorders and Stroke, NIH, Bethesda, MD

Abstract: Multiple sclerosis (MS), an autoimmune disease of the central nervous system, is characterized by inflammation, demyelination, and varying degrees of neurodegeneration. In some patients this neurodegeneration can be chronic and intractable, leaving patients with profound disability. Here, we investigate a relatively understudied aspect of neurodegenerative MS pathology: alterations in synaptic connectivity. Using the retinogeniculate system, a circuit that is frequently affected by optic neuritis and therefore highly relevant to MS patients, we show in postmortem human MS tissue, a nonhuman primate MS model, and two rodent models of demyelination that synapses are significantly reduced and microglia engulf large amounts of presynaptic material. Using animal models, we then show that these events can occur independent of local demyelination and axonal degeneration, but coincide with gliosis and the deposition of complement factor C3, but not C1q, at synapses. Finally, using a novel AAV strategy to specifically inhibit activated complement at the synapse we show that we can protect synapses from elimination and preserve visual function. Ultimately, this approach could be used

to prevent synapse loss by microglia with very high spatial and temporal precision in human patients, and may be broadly applicable to other neurodegenerative diseases, including Alzheimer's disease, where microglia and complement have been implicated.
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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: SAF2014-56671-R from Ministerio de Economía y Competitividad of Spain
PNSD001I2015 from National Plan on Drug abuse, Ministerio de Sanidad, Servicios Sociales e Igualdad of Spain

Title: Receptor protein tyrosine phosphatase beta/zeta regulates microglial activation: Evidence for a neuroprotective response of microglia through upregulation of pleiotrophin, not midkine

Authors: *G. HERRADON, M. GABRIEL, R. FERNÁNDEZ-CALLE, A. RAMIREZ, J. M. ZAPICO, A. RAMOS, B. DE PASCUAL-TERESA, E. GRAMAGE;
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Abstract: Pleiotrophin (PTN) and Midkine (MK) are neurotrophic factors that exert neuroprotective effects and limit glial responses in animal models of Parkinson's disease (PD). PTN and MK signal through different receptors including Receptor Protein Tyrosine Phosphatase (RPTP) β/ζ, which is abundantly expressed in the CNS. They bind to RPTPβ/ζ and inhibit its phosphatase activity, causing increases in tyrosine phosphorylation of RPTPβ/ζ substrates that are involved in neuroprotection. To test the possible role of RPTPβ/ζ in microglial activation, we treated BV2 cells (mouse microglia) with Lipopolysaccharide (LPS) and the recently developed RPTPβ/ζ inhibitors MY10 and MY33-3. Both inhibitors reduced LPS-induced microglial release of nitric oxide (NO) and LPS-induced increases of iNOS mRNA levels. In contrast, inhibition of RPTPβ/ζ potentiated LPS-induced increase of TNF-α mRNA levels whereas it did not cause significant changes in COX-2 levels. The results demonstrate an important role of RPTPβ/ζ in microglial activation. Since PTN/MK, the RPTPβ/ζ endogenous inhibitors, play important roles in PD and neuroinflammation, we aimed to assess the possible

role of RPTPβ/ζ in an *in vitro* model of neuronal injury. Neuroblastoma SH-SY5Y cells were treated with the parkinsonian toxin MPP+ and MY10. MPP+ induced a significant decrease of SH-SY5Y cell viability whereas co-treatment with MY10 did not cause relevant effects. When BV2 cells were incubated with the conditioned media from SH-SY5Y cells treated with MPP+ and/or MY10, we observed a significant decrease in the viability of BV2 cells incubated with the media from SH-SY5Y cells treated with MPP+, but no apparent influence of co-treatment with MY10 was detected. Interestingly, in BV2 cells incubated with the media from SH-SY5Y cells treated with MPP+, we detected a highly significant increase of *Ptn* mRNA levels, which was attenuated in BV2 cells incubated with the media from SH-SY5Y cells treated with MPP+ and the RPTPβ/ζ inhibitor MY10. In contrast *Mk* levels in BV2 cells were not affected by any treatment. The data indicate that the media from SH-SY5Y cells treated with MPP+ decreases microglia viability but may elicit a neuroprotective response of microglia by inducing a significant increase of microglial *Ptn* levels.

Disclosures: G. Herradon: None. **M. Gabriel:** None. **R. Fernández-Calle:** None. **A. Ramirez:** None. **J.M. Zapico:** None. **A. Ramos:** None. **B. de Pascual-Teresa:** None. **E. Gramage:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.04/G21

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: MOST 107-2320-B-006-015

Title: Chronic high fat diet feeding suppresses microglia activation and anxiety induced by intermittent exposures to lipopolysaccharides

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Abstract: Gliosis, a reactive change of astrocytes and microglia, is observed in the hypothalamus (HT) of obese rodents and humans. In the recent study, using high-fat diet (HFD)-fed animal model, we have observed that HFD feeding caused prolonged microgliosis in arcuate nucleus (ARC) of HT. To investigate if environmental stress stimuli can augment HFD-fed mice to develop emotional disorder, intermittent peripheral inflammagen (lipopolysaccharide; LPS) challenge (iLPS) were conducted during the onset period of HFD feeding. Male mice received 1 mg/kg of LPS (or saline) by i.p. route at week 1, week 2, and week 8 after Chow (iLPS+Chow) or HFD (iLPS+HFD) feeding. Through QPCR analysis, we found that hypothalamic IL1-β and

TNF-α mRNA levels were upregulated at 24 hour after the initial injection of LPS (1 week). Although no difference in the expression of these cytokines was detected at 24 hour after the second-time LPS injection, the upregulation of IL-1β and TNF-α was detected at 24 hour after third-time LPS injection (8 week). These findings suggest that intermittent LPS injection can elevate the expression of proinflammatory cytokines in HT. Subsequently, the animals (saline+Chow, saline+HFD, iLPS+Chow, iLPS+HFD) were continuously fed by either Chow or HFD up to 5 month. Immunofluorescence for examination of microglia in emotion related brain regions including nucleus accumbens (NAc), anterior cingulate cortex (ACC), insula, and basolateral amygdala (BLA) showed that activated microglia were found in BLA, insula, and ACC of the iLPS+Chow group when compared to saline+Chow. Moreover, an increased cell body size of microglia was detected in NAc, ACC, and insula of the saline+HFD group when compared to those of the Chow+saline group. Interestingly, the combination of iLPS with HFD attenuated microglia activation induced by iLPS+Chow or saline+HFD in the indicated brain regions. Through animal behavioral tests, we found that the iLPS+Chow group developed abnormal anxious behavior, whereas chronic HFD feeding can lessen iLPS-induced anxiety. Thus, our findings demonstrate that chronic HFD feeding can reduce iLPS-induced microglia activation in emotion-related brain regions, possibly leading to diminishing iLPS-triggered anxiety development in mice.

Disclosures: H. Huang: None. **Y. Kuo:** None. **P. Chen:** None. **S. Tzeng:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.05/G22

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Microglial responses to citrullinated self and non-self proteins

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Abstract: Citrullination, also known as deimination, is a post-translational modification whereby arginine residues are irreversibly converted into citrulline. Citrullination has been implicated in several autoimmune conditions, including multiple sclerosis (MS). While citrullinated proteins, particularly citrullinated myelin basic protein (MBP), have been shown to be upregulated in MS, the consequences of this modification with regard to MS are unknown. Citrullination may alter-self peptide immunogenicity by changing how these peptides bind to MHC molecules or T cell receptors. Additionally, it is unknown if citrullinated peptides can activate microglia, the resident phagocytes and innate immune cells of the brain. We show that citrullinated myelin debris drives a microglial phenotype characterized by activation of pro-inflammatory signaling pathways that

ultimately results in the release of pro-inflammatory cytokines and chemokines. We demonstrate that this microglial response is not only specific to citrullinated MBP but is partially mimicked by citrullinated viral proteins. These findings suggest a common mechanism whereby a citrullinated peptide sequence derived from either virus or myelin may contribute to innate immune activation and neuroinflammation in MS.

Disclosures: M.M. Standiford: None. **E.M. Grund:** None. **C.L. Howe:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.06/G23

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Comparative study among the anti-inflammatory supplementation on microglial cells

Authors: *M. SAKAI[1], H. TOMITA[2,4], Z. YU[4,3];
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Abstract: Activated microglia are polarized two phenotypes M1 and M2, which are known to release inflammatory factors, anti-inflammatory cytokine and neurotrophic factors to maintain homeostasis of brain. Microglia producing TNF-α plays an important role in the sustained fear memory. Previous investigations have demonstrated that minocycline inhibits M1 type microglial activation. We reported that pretreated minocycline inhibited fear memory retention induced TNF-α production and enhances fear memory extinction, indicates that drugs that inhibit TNF-a production may be beneficial for the treating patients with post-traumatic stress disorder (PTSD). Despite women appear to be more susceptible than men to PTSD, administration of minocycline causes severe side effects in women, which is urgently needed to find safety and efficacy of supplementation in PTSD treatment. This study due to compare the effects of anti-inflammatory supplementations which could inhibit M1 microglia activation. Four kinds of supplementations: vitamin E (VE), α Lipoic-acid (α-LA), N-acetyl carnitine (NAC) and Acetyl-L- carnitine (ALCAR), with small molecular weight that can pass through blood-brain barrier, which anti-inflammatory activation have been reported. Four supplementations were administered to the microglial cell line MG-6 to examine the inhibitory effects on increased microglial inflammatory activation by LPS stimulation. Our results showed that NAC inhibited LPS induced Tnf and Il1 at both transcription and protein levels, whereas increased IL10, IL4 transcription levels. ACLAR and alpha-LA, inhibited Tnf and Il1transtription levels but did not reach significance. Recent studies indicated that inhibited apoptosis associated gene BCL2 by IL-10. In particular, NAC significantly reduced microglial TNF-α by induced Il10 transcription.

Our finding indicated that NAC as a potent supplement which may use for anti-inflammatory supplement in CNS, which could be useful for PTSD treatment.

Disclosures: **M. Sakai:** None. **H. Tomita:** None. **Z. Yu:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

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Program #/Poster #: 477.07/G24

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIEHS Grant ES007062-20

Title: Investigating the functional significance of TSPO-NOX2 interaction in primary microglia

Authors: D. J. AZZAM[1], V. NUNES DE PAIVA[1], S. GUARIGLIA[2], *T. R. GUILARTE[1]; [1]Envrn. Hlth. Sci., Florida Intl. Univ., Miami, FL; [2]New York State Inst. for Basic Res., Staten Island, NY

Abstract: Translocator protein 18 kDa (TSPO) is a biomarker of brain injury and inflammation that has been extensively used in preclinical and clinical studies. TSPO is expressed in microglia and astrocytes, and TSPO levels increase rapidly following diverse CNS pathologies. NADPH Oxidase (NOX2) is a multi-subunit enzyme that is highly expressed in microglia and is a major source of ROS production in the CNS. We have previously shown a direct protein-protein interaction between TSPO and NOX2 subunits in primary microglia (Loth et al., SfN Annual Meeting, 2017). The functional significance of this novel interaction is not known but may involve modulation of reactive oxygen species (ROS) production in microglia with important implications to neuroinflammation and neurodegeneration. To determine if deletion of TSPO would modify the expression of NOX2 subunit genes, we generated primary microglia from TSPO-wildtype (WT), -heterozygous (HET), and -knockout (KO) mice. Levels of mRNA expression for *Tspo* and the *Nox2* subunits *gp91phox*, *p22phox*, *p40phox*, *p47phox*, *p67phox*, and *Rac1* were measured using qRT-PCR. We also measured *Vdac* mRNA expression as a mitochondrial marker since TSPO is highly expressed in mitochondria. We found a TSPO gene dosage effect on *Tspo* mRNA expression in primary microglia that was confirmed at the protein level. Importantly, mRNA expression of the *Nox2* subunits *gp91phox*, *p22phox*, and *p67phox* were significantly decreased in microglia from TSPO-KO mice with no effect on *p40phox*, *p47phox*, and *Rac1*. No significant effect of TSPO gene deletion was found on *Vdac* gene expression levels. These findings suggest transcriptional regulation of specific NOX2 subunit genes by TSPO gene deletion. Ongoing studies are determining the effect of TSPO deletion on NOX2 subunit protein expression and enzymatic activity. Based on our previous identification of a novel TSPO-NOX2 interaction and a putative increase in TSPO surface expression in activated

microglia, we determined if modulating ROS production would alter the subcellular distribution of TSPO in primary microglia. We found that exposure of primary microglia to the ROS inducer tert-butylhydroperoxide (TBHP) increased the cell surface expression of TSPO from approximately 13% under basal conditions to over 30% in the presence of TBHP. This effect of TBHP was abrogated by the ROS scavenger N-acetyl cysteine (NAC). Our findings suggest for the first time that TSPO, known as a mitochondrial protein, can increase its surface expression in microglia under conditions of increased ROS production. This effect may be associated with a functional TSPO-NOX2 interaction.

Disclosures: **T.R. Guilarte:** None. **D.J. Azzam:** None. **S. Guariglia:** None. **V. Nunes de Paiva:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Defense Medical Research
Development Program 0130-10-00003-00002
Defense Health Agency 0130-18-0003-00017
NHLBI/USU Collaborative Health Initiative Research Program 308431-9.00-64532

Title: Inhibition of fatty acid amide hydrolase suppresses inflammation in LPS-activated BV2 microglial cells

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Abstract: Fatty acid amide hydrolase (FAAH) is an integral membrane enzyme and belongs to a large serine hydrolase family. Numerous studies have suggested that FAAH represents a potential therapeutic target for several neurological diseases, since its inhibition can exert neuroprotective and anti-inflammatory effects by boosting the endogenous levels of N-acylethanolamines (NAEs) including endocannabinoid anandamide (AEA). However, the role of FAAH in the inflammatory response and the mechanisms by which pharmacological inhibition suppresses inflammation have not been well-elucidated in reactive microglia. In this study, we analyzed the effects of two commonly used FAAH inhibitors PF-3845 and URB597, together with siRNA knockdown to characterize FAAH inhibition on lipopolysaccharide (LPS)-induced inflammation in BV2 microglia cells. Treatment with PF-3845 suppressed LPS-induced

prostaglandin E_2 (PGE_2) production along with downregulation of cyclooxygenase-2 (COX-2) and microsomal PGE synthase. PF-3845 reduced the expression of pro-inflammatory cytokines such as IL-6 and IL-1β, but had no effects on the expression of anti-inflammatory cytokines. The anti-inflammatory effect of URB597 was not as potent as that of PF-3845. FAAH knockdown also suppressed PGE_2 production and pro-inflammatory gene expression. Surprisingly, the knockdown of FAAH enhanced anti-inflammatory gene expression such as IL-4 and IL-10 in the absence or presence of LPS treatment. Furthermore, Cannabinoid receptor antagonists did not affect the above-mentioned phenomena, suggesting that the effects of the FAAH are independent of cannabinoid receptors. Together, these results indicate that the dynamic change of M1 to M2 microglia polarization might underlie the therapeutic effect of targeting FAAH in several neurological and neuropsychiatric diseases.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro
Conselho Nacional de Desenvolvimento Científico e Tecnológico
National Institute for Translational Neuroscience
Human Frontiers Science Program
John Simon Guggenheim Foundation

Title: Palmitate increases microglia-derived TNF-alpha levels and impairs hippocampal insulin signaling

Authors: *H. M. MELO[1], G. SEIXAS DA SILVA[2], B. C. DE MELO[1], J. T. S. FORTUNA[1], S. T. FERREIRA[1], F. G. DE FELICE[1];
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Abstract: Unhealthy diets and poor lifestyle habits are related to an increasing burden of metabolic disorders worldwide, including type 2 diabetes (T2D) and obesity-related insulin resistance. T2D and obese patients exhibit cognitive impairment and increased risk of developing dementia. However, the fundamental mechanisms underlying these clinical observations remain largely unknown. Elevated levels of free fatty acids in the circulation is linked to metabolic dyshomeostasis and peripheral insulin resistance, especially saturated fatty acids (SFA), such as

palmitate. Interestingly, brain palmitate uptake is increased in obese patients, with a positive correlation with aging. Thus, to understand how excessive levels of SFAs could impact brain function, we investigate the impact of palmitate, the most abundant circulating SFA, on the hippocampus, an important brain region for learning and memory. Interestingly, infusion of palmitate into the lateral cerebral ventricle of mice led to microglial activation and increased tumor necrosis factor alpha (TNF-alpha) levels in the hippocampus. In addition, palmitate reduced insulin expression and induced neuronal insulin receptor substrate 1 (IRS-1) phosphorylation at multiple inhibitory serine residues in primary hippocampal cultures. Importantly, palmitate failed to cause insulin signaling impairment in the presence of minocycline or infliximab, which inhibits microglial activation and neutralizes TNF-alpha, respectively. Altogether, our results delineate a pro-inflammatory mechanism underlying the deleterious effects of palmitate on neuronal insulin signaling, a pathway centrally involved in the learning and memory process in the brain. In addition, our findings contribute to the understanding of how unhealthy diets and metabolic disorders render the brain susceptible to memory defects and to dementia.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.10/G27

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: 7,8-dihydroxyflavone prevents 3-nitropropionic acid induces striatal toxicity by modulating the TrkB receptor and microglial activation pathway

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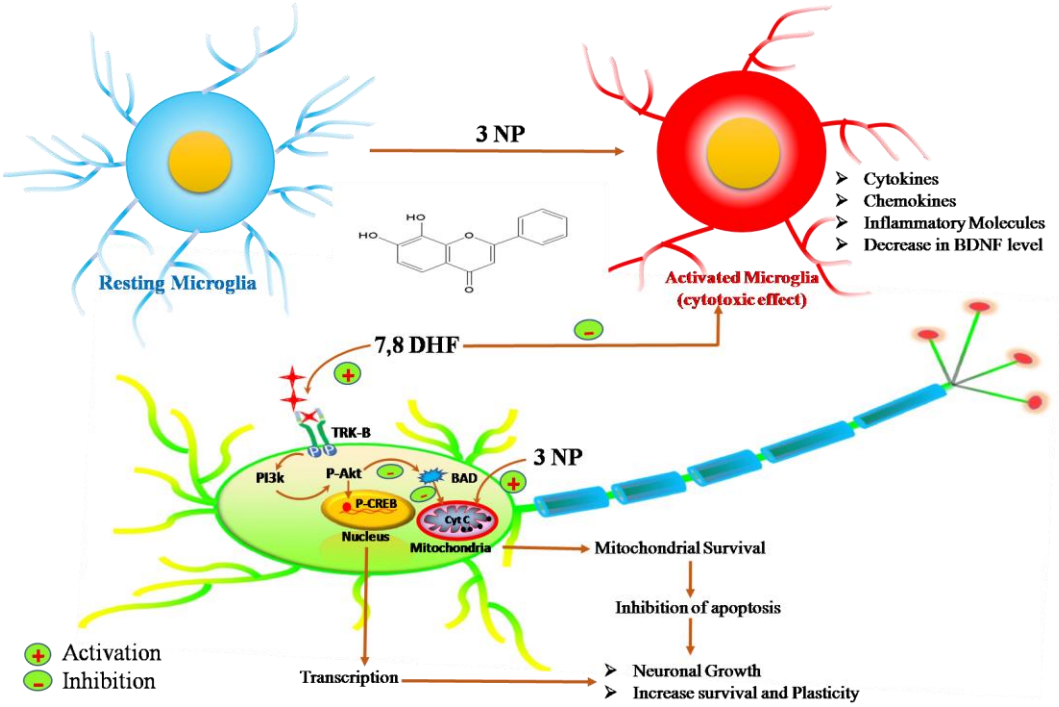
Abstract: Huntington’s disease (HD) is an autosomal governing neurodegenerative disorder caused by production of mutant huntingtin(Htt) protein followed by death of the GABAergic neurons in the striatum. These neurons depend on an afferent supply of brain derived neurotrophic factor-(BDNF) which binds to its tropomyosin receptor kinase B (TrkB) receptor for maintaining plasticity, differentiation and survival. Impaired BDNF-TrkB signaling is assumed to be the mechanism underlying degeneration of neurons in HD. Therefore, we aimed to investigate an active molecule which mimics similar to BDNF in activating the TrkB receptor and its downstream pathway. 7,8-Dihydroxyflavone (7,8-DHF), has a better BBB penetrating ability and our results stated the treatment with 7,8-DHF causes a dose dependent manner activity in ameliorating the various behavior alterations caused by 3-nitropropionic acid (3-NP).

Histopathological and electron microscopy evidences from striatal region of 3-NP mice brain treated with 7,8-DHF showed more healthier neurons with intact mitochondrial morphology and very less autophagic vacuoles. These protections by 7,8-DHF may be due to an increase level of ATP which in turn down regulates cytochrome c releases from the mitochondrial matrix and inactivates Bad protein activation. It also enhanced the BDNF levels by promoting cAMP response element-binding protein (CREB) activation. Moreover, it showed an anti-inflammatory as well as anti-apoptotic potential with reduction in Iba-1, Cox-2 and Bcl-2 expression levels. 7,8-DHF also enhances phosphorylation of TrkB (Ty706) and Akt (Ser473/Thr308) and promotes its downstream signaling cascades in 3-NP induced striatal toxicity in experimental mice which might be the mechanism for its striatal neurons protection.



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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.11/G28

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: The NF-kB transcriptional factor modulates microglia activation

Authors: *H. CHOI[1], G. AHN[1], M. BAEK[2], K. JUNG[4], Y. CHAI[3];
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Abstract: The transcription factor (TF) nuclear factor-kB (NF-kB) plays a critical role in regulating the neuroinflammation in microglia. NF-kB family is composed of NF-kB1 (p50), NF-kB2 (p52), RelA (p65), RelB and cRel, which mediates production and secretion of various pro-inflammatory genes, cytokines, and chemokines. To address the role of transcriptional responses in microglia cells, we established p65 knock-out (KO) microglia BV2 cell line and studied the immune-modulatory effects using RNA-seq analysis. The gene expression profile was performed with BV2 control, lipopolysaccharide (LPS)-treated BV2 control, p65 KO BV2 and LPS-treated p65 KO BV2. Using differentially expressed genes (DEGs), we identified downregulated patterns of interferon-stimulated genes, cytokines, and chemokines. Moreover, we further analyzed DEGs to identify transcriptional motifs (-950 bp to +50 bp of the 5' upstream promoters) and epigenetic modification. TF motif analysis revealed that the DNA sequences for Stat1/2, Irf1, Irf7, Irf9 were significantly enriched in downregulated genes in LPS-treated p65 KO BV2 cells. Also, those genes were reduced H3K27ac level in their promoter. Taken together, these results provide the p65 orchestrates the LPS-stimulated immunomodulatory response of BV2 involved in Stat1, Irf1, Irf7, Irf9, and histone modification (H3K27ac).

Disclosures: H. Choi: None. **G. Ahn:** None. **M. Baek:** None. **K. Jung:** None. **Y. Chai:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.12/G29

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: R01 EY07060

Title: Exploring the mechanisms that govern microglia dynamics during photoreceptor cell death and regenerative neurogenesis in zebrafish

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Abstract: Understanding the mechanisms that govern regenerative neurogenesis will advance the field of stem cell-based therapies. Increasing evidence shows that acute inflammation is

necessary and sufficient for the neurogenic response of neural stem cells. Chronic inflammation, however, is detrimental. Microglia are endogenous immune cells of the macrophage lineage within the central nervous system that secrete cytokines and chemokines, which function to govern inflammation. In the zebrafish retina, Müller glia serve as intrinsic stem cells that, in response to neuronal death, dedifferentiate and undergo a single asymmetric division to produce retinal progenitors, which rapidly proliferate, migrate and differentiate to replace the ablated neurons. In this study, we used the mutant zebrafish, *midkine-a*^{mi5001}, which has a loss-of-function mutation in *midkine-a*, which encodes a growth factor/cytokine that has multiple functions in neural development, inflammation, and disease. We investigated the molecular mechanisms by which microglia mediate inflammation during the selective death and regeneration of photoreceptors. In wildtype retinas following a photolytic lesion, photoreceptors become TUNEL-positive by 1 day post lesion (dpl). Nearby microglia respond to the cell death rapidly and by 3 dpl phagocytose the dying photoreceptors. In the mutant retina, the time course of photoreceptor cell death and microglial activation is unaltered, however, activated microglia fail to phagocytose dying photoreceptors, resulting in dysregulation in the expression of inflammatory cytokines. These data suggest that Midkine-a orchestrates inflammatory status of the damaged retina by mediating communication between dying photoreceptors and microglia.

Disclosures: M. Nagashima: None. **P.F. Hitchcock:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.13/G30

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: MU Research Office

Title: Quantitative proteomics reveals docosahexaenoic acid-mediated neuroprotective effects in lipopolysaccharide-stimulated microglial cells

Authors: *C. M. GREENLIEF[1], B. YANG[3], R. LI[4], X. GENG[7], B. MOONEY[5], K. L. FRITSCHE[6], D. Q. BEVERSDORF[2], J. C. LEE[8], G. Y. SUN[9];
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Abstract: The high level of docosahexaenoic acid (DHA) in phospholipids in the brain has spurred significant interest in its role in brain health and diseases. Recent studies provided evidence for DHA to play a role in inhibiting inflammatory responses in microglial cells,

although the mechanism(s) remains elusive. In this study, a global proteomic approach was used to examine effects of DHA on microglial cells stimulated with lipopolysaccharides (LPS). Deep proteome coverage was achieved using the parallel accumulation serial fragmentation (PASEF) method in a hybrid trapped ion mobility spectrometry (TIMS) - quadrupole time-of-flight mass spectrometer (TIMS-ToF). Using label-free quantitative proteomics, a total of 2858 protein groups (with more than one unique peptide) were confidently identified and quantified in BV-2 microglial cells. Treating the cells with LPS and/or DHA altered cell morphology and expression of 43 proteins with a differential abundance (greater than 2.0-fold change). Bioinformatic analyses further indicated that these differentially abundant proteins were involved in the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, fatty acid metabolism, mitochondrial activity, response to bacterium, cytoskeleton, DNA binding, and ribosome biogenesis. Quantitative analyses of cell viability, tumor necrosis factor alpha, phospho-NF-κB p65, inducible nitric oxide synthase and prostaglandin E2 expression levels were consistent with the biological outcomes of the altered protein concentrations. Together, these data indicate for the first time multiple mechanisms of DHA-mediated protective effects in LPS-stimulated BV-2 microglial cell at the global proteome level. This information may shed light on a new basis for therapeutic strategies of DHA against inflammation.

Disclosures: C.M. Greenlief: None. **B. Yang:** None. **R. Li:** None. **X. Geng:** None. **B. Mooney:** None. **K.L. Fritsche:** None. **D.Q. Beversdorf:** None. **J.C. Lee:** None. **G.Y. Sun:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.14/G31

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Decoding the role of P2X7 in neuroinflammation

Authors: *R. C. GRUBER[1], L. WOODWORTH[1], J. GANS[2], J.-M. CHAMBARD[3], K. SINGH[4], D. BANGARI[4], T. SAMAD[1], D. OFENGEIM[1];
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Abstract: Background: Neuroinflammation has been implicated in many disorders of the central nervous system, in particular Multiple Sclerosis (MS). Active MS lesions exhibit demyelination and oligodendrocyte loss, as well as infiltration with CD68+ macrophages, microglia and lymphocytes. Within active lesions, axons are largely devoid of myelin, and are vulnerable to injury. P2X7 is a purinergic receptor activated by high levels of ATP and is

expressed by macrophages and several cell types of the CNS, including microglia and oligodendrocyte precursor cells (OPCs). While extracellular ATP levels are typically low, cytosolic concentrations of ATP range between 5 and 10mM. Therefore, CNS insults such as inflammation, trauma, stroke, and neurodegeneration can cause a marked release of intracellular ATP into the extracellular space, making ATP an important danger signal. While it is clear that P2X7 activation contributes to the release of IL-1β and other inflammatory cytokines, P2X7 downstream signaling and the consequences therein remain unclear. **Objective:** To characterize the downstream signaling of P2X7 in microglia and assess whether inhibition of P2X7 activation in the CNS reduces central inflammation, and attenuates disease pathology. **Results:** We studied a microglial P2X7 activation signature by using BzATP as the activation stimulus in the presence or absence of a P2X7 antagonist. We have compared this signature to previously published microglial signatures and have identified genes that are partially and fully inhibited by a P2X7 allosteric inhibitor. We further validated select P2X7 signature genes in human primary macrophages. Finally, we observe therapeutic efficacy of a P2X7 antagonist in an experimental autoimmune encephalomyelitis (EAE) mouse model of MS, with a corresponding reduction in demyelinating lesions and plasma neurofilament heavy (NFH), as a potential biomarker of axonal injury. **Conclusion:** We have established a P2X7 microglial signature and demonstrated *in vivo* activity using a P2X7 allosteric inhibitor. In summary, the microglial signature along with *in vivo* activity demonstrate the validity of P2X7 as a target for central inflammation and shed light on the inflammatory signaling downstream of P2X7.

Disclosures: **R.C. Gruber:** A. Employment/Salary (full or part-time):; Sanofi. **L. Woodworth:** A. Employment/Salary (full or part-time):; Sanofi. **J. Gans:** A. Employment/Salary (full or part-time):; Sanofi. **J. Chambard:** A. Employment/Salary (full or part-time):; Sanofi. **K. Singh:** A. Employment/Salary (full or part-time):; Sanofi. **D. Bangari:** A. Employment/Salary (full or part-time):; Sanofi. **T. Samad:** A. Employment/Salary (full or part-time):; Sanofi. **D. Ofengeim:** A. Employment/Salary (full or part-time):; Sanofi.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.15/G32

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant EY10343
NIH Grant R56 DE023806
The Michael Reese Foundation
Catalyst Award from the Chicago Biomedical Consortium
LASURI Grant
Honors College Undergraduate Research Grant

NIH Core Grant P30 EY001792

Title: Functionally engineered extracellular vesicles derived from mesenchymal stem-cells provide neuroprotection by attenuating microglia activation in retinal ischemia

Authors: *R. PATEL[1], B. MATHEW[1], S. RAVINDRAN[2], C.-C. HUANG[2], M. CHENNAKESAVALU[1], L. GAMBOA ACHA[1], S. ROTH[1];
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Abstract: Many retinal diseases involve loss or dysfunction of multiple types of retinal neurons, endothelial cells, and pericytes leading to oxidative stress, inflammation, and retinal ischemia. Retinal inflammation with activated retinal microglia (RMG) is major event in diabetic retinopathy. Our previous studies using a rat model of retinal ischemia have demonstrated robust neuroprotective effects of MSCs derived extracellular vesicles (EVs) when injected in the vitreous. MSCs produce extracellular vesicles (EVs) which are specifically involved in intercellular communication and are capable of transferring protein and nucleic acids between cells. The neuroprotective effects of MSCs appear to be largely mediated by EVs in retinal ischemia and are related to anti-apoptosis and anti-inflammatory actions, as shown in recently published studies. Preliminary data suggests that this neuroprotection is in part due to the RMG uptake of MSC-EVs. MSC-EVs appear to suppress the activation of RMG. RMG are the resident macrophages of the neuronal tissue capable of inducing cell proliferation through their activation upon injury; however, RMG exacerbate the situation by releasing toxic and pro-inflammatory compounds, particularly cytokines. RNA Seq analysis indicated miR-424 as one of the primary anti-inflammatory miRNAs in MSC-EVs. Anti-inflammatory effects of MSC-EVs can be enhanced by generating Functionally Engineered EVs (FEEs) containing increased levels of miR-424. In this study we have developed engineered EVs containing increased levels of miR-424. EVs were isolated from MSC conditioned media and characterized by Western Blot (WB), Nanoparticle Tracking Analysis, and Transmission Electron Microscopy. *In vitro*, the cultured RMGs were pre-incubated for 24h with EVs or FEE miR-424 and subjected to Oxygen Glucose Deprivation (OGD) with experimental groups: OGD, OGD+MSC-EVs/FEE miR-424, and OGD+CM minus EVs/FEE miR-424 as the control. The outcomes were measured by evaluating cell death (LDH), inflammatory cytokines, nitric oxide levels (NO) and ROS measurements. MSC enhanced FEE-miR424 confer significant neuroprotective effects *in vitro*. This study demonstrates that FEEs miR-424 suppresses RMG activation.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.16/G33

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant R01AG041944

Title: A focused transcriptome of aging-associated, immune-driven cognitive failure reveals distinct patterns hippocampal gene expression in aged vs. young rats following an acute immune challenge

Authors: *L. DEFLITCH, C. R. FITZGERALD, B. METENKO, N. TANAKA, S. L. PATTERSON, H. E. ANNI;
Biol., Temple Univ., Philadelphia, PA

Abstract: Aging increases the risk of an abrupt cognitive decline, termed delirium, following an injury or illness. An episode of delirium is associated with a greater risk of developing Alzheimer's disease and other forms of dementia, yet very little is known about the underlying mechanisms. Data from rodent models suggests that aging primes cells of the innate immune system in the brain to produce a dysregulated response to immune challenges. Aged (24-month-old) Fischer Brown Norway (F344xBN) rats are generally healthy with no major physical or cognitive deficits. However, following a single i.p. injection of *E. coli*, these aged rats mount an exaggerated CNS inflammatory response (e.g. greater production of proinflammatory cytokines, like IL-1β) relative to young (3-month-old) rats, leading to deficits in hippocampus-dependent long-term memory and related synaptic plasticity.
To further investigate how age and an immune challenge can compromise the capacity for memory-related synaptic plasticity, we are now using NanoString multiplex gene expression analysis of whole hippocampal extracts and hippocampal synaptoneurosomes. Screening samples against a curated gene expression panel of over 700 genes makes it possible to more closely examine differences in how the brains of young and aged animals respond to an acute immune challenge, and how these differences may contribute to immune-driven cognitive failures like delirium. The genes of the panel were selected for involvement in immune responses, neuron-glia interactions, synaptic plasticity and related memory functions. Our preliminary data show changes in expression of a number of microglial activation- and cytokine-related genes, genes related to autophagy, glial- and neurogenesis, and genes related to neurotransmitter synthesis and storage.
We are using a time-course to study whether aged animals display different inflammatory mechanisms from young animals or if their mechanisms are similar but follow a delayed time course. Animals are sacrificed and their mRNA extracted at two time points after the *E. coli*

injection: either one day, while animals are still physically ill, or four days, when animals are physically recovered, (i.e. no fever, normal eating) post-infection. Studying the gene expression patterns throughout this time-course of inflammatory response should increase our understanding of how an acute immune challenge can compromise cognitive function in aged brains.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.17/G34

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Title: Suppression of microglia mediated neuroinflammation by small molecule NFκB inhibitors

Authors: B. ASTRY, R. GRANT, *K. BRADLEY, K. BRUMBAUGH, J. RIVARD, M. CARLSON-HABEGGER, M. LARSON, **J. KIRK**, A. HUDACEK, G. WEGNER;
R&D Systems, Bio-techne, Minneapolis, MN

Abstract: It has been shown that long-term production of proinflammatory cytokines by activated microglia plays a role in neurodegenerative disorders like Parkinson's disease and multiple sclerosis. Here we investigated if inhibition of the NFκB signaling pathway, an important factor in the inflammatory response, could alter the chemokine and cytokine profile of the BV-2 mouse microglia cell line. Using the Toll-like Receptor 4 (TLR4) agonist lipopolysaccharide (LPS), we stimulated BV-2 cells and subsequently treated them with two different small molecule inhibitors, MLN4924 (a NEDD8 E1 Activating Enzyme inhibitor) and Celastrol (a NFκB inhibitor). Cell supernatants and lysates were measured for 48 mouse cytokines/chemokines/growth factors using the R&D Systems® Mouse Magnetic Luminex® Assay. LPS stimulation increased multiple proinflammatory cytokines, including IL-1α/IL-1F1, IL-1β/IL-1F2, IL-6, IL-27, and TNF-α, and the chemokines CCL4/MIP-1β, CCL5/RANTES, CXCL1/KC and CXCL10/IP-10/CRG-2. Treatment with either MLN4924 or Celastrol resulted in significant decreases in the levels of the proinflammatory cytokines and chemokines. We then investigated if MLN4924 and Celastrol act by inhibiting the canonical and/or non-canonical NFκB signaling pathway. We showed that MLN4924 and Celastrol inhibited IκB-α degradation and MLN4924 inhibited p100 degradation. This indicates that these small molecules act by inhibiting NFkB signaling. In addition, MLN4924 also preserved RelA/NFκB p65 phosphorylation and reduced ubiquitination of TNF R1/TNFRSF1A. These results suggest the small molecule inhibitors MLN4924 and Celastrol can be used to suppress microglia-mediated neuroinflammation.

Disclosures: **B. Astry:** A. Employment/Salary (full or part-time):; Bio-Techne. **R. Grant:** A. Employment/Salary (full or part-time):; Bio-Techne. **K. Bradley:** A. Employment/Salary (full or part-time):; Bio-Techne. **K. Brumbaugh:** A. Employment/Salary (full or part-time):; Bio-Techne. **J. Rivard:** A. Employment/Salary (full or part-time):; Bio-Techne. **M. Carlson-Habegger:** A. Employment/Salary (full or part-time):; Bio-Techne. **M. Larson:** A. Employment/Salary (full or part-time):; Bio-Techne. **J. Kirk:** A. Employment/Salary (full or part-time):; Bio-Techne. **A. Hudacek:** A. Employment/Salary (full or part-time):; Bio-Techne. **G. Wegner:** A. Employment/Salary (full or part-time):; Bio-Techne.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.18/G35

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Funds from the State of Florida

Title: Lipopolysaccharide or Il-1β microglial inflammasome activation bi-directionally alters morphine reward in a time-dependent manner sensitive to anti-inflammatory interventions

Authors: ***A. R. ALLEYNE**[1], T. J. CIRINO[1], S. O. EANS[1], H. M. STACY[1], P. ZHANG[1], S. STEVENS[2], B. LIU[1], J. P. MCLAUGHLIN[1];
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Abstract: Neuroinflammation has been shown to both suppress and potentiate the rewarding effects of abused substances like morphine, but the underlying mechanisms are poorly understood. We hypothesize that microglia inflammasome activation upregulates inflammatory cytokines in the CNS that mediate bidirectional changes in reward circuitry. To test this, C57BL/6J (C57) mice and secreted phosphoprotein 1 gene-disrupted (SPP1 KO) mice, a C57 strain possessing impaired microglial activity, were used in a model of brain-exclusive inflammation produced by i.c.v. administration of lipopolysaccharide (LPS, 100 ng) prior to morphine treatment in a morphine-conditioned placed preference (CPP) assay. C57 mice showed time-dependent alterations in morphine CPP. A 45 min. LPS pretreatment decreased morphine CPP 88%, whereas a 90 min. LPS treatment resulted in a 3 fold increase in morphine place preference. SPP1 KO mice and C57 mice pre-treated with the anti-inflammatory agent, indomethacin (10mg/kg, i.p.) prior to LPS, showed no change in morphine preference at either time point. Using a two-bottle choice (TBC) assay, voluntary consumption of morphine in C57 mice treated with LPS (0.3 mg/kg/d, i.p.) was reduced up to 80% as compared to vehicle-treated mice, but returned to normal in two days. Further demonstrating the involvement of inflammatory cytokines, a 90 min pre-treatment of C57 mice with interleukin-1β (IL-1β;

2µg/kg/d i.p.) prior to daily morphine-place conditioning resulted in a two-fold increase in morphine CPP that was blocked by indomethacin. Histological studies utilizing immunohistochemistry (IHC) and Western Blot techniques evaluated morphological and established marker expression (Iba1, TMEM119 and GFAP) of gliosis within the reward pathway (nucleus accumbens (NAc), ventral tegmental area (VTA), and pre-frontal cortex (PFC). Additional studies evaluated inflammasome activation in brain microglia. Preliminary data suggests a time- and dose-dependent alteration in microglia count and morphology in a brain region-specific manner which is differentially sensitive to SPP1 gene disruption. Overall, these results enhance our understanding of the bi-directional influence of neuroinflammation on morphine reward, and may identify novel therapeutic treatments for opioid addiction.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: The Dr Miriam and Sheldon G Adelson Foundation in Neurorepair and Rehabilitation
NIH R01 NS081281

Title: Role of microglia in immune mediated retinal ganglion cell protection and axon regeneration

Authors: *R. PASSINO, C. YOON, L. HUFFMAN, O. NELSON, B. SEGAL, R. GIGER; Univ. of Michigan, Ann Arbor, MI

Abstract: In adult mammals, retro-orbital optic nerve crush injury (ONC) results in retinal ganglion cell (RGC) death and failure of severed axons to regenerate beyond the lesion site. Under certain circumstances, however, activation of the innate immune system leads to robust RGC protection and axon regeneration. For example, intraocular injection (i.o.) of zymosan or mechanical damage to the ocular lens triggers an immune response that protects injured RGCs and promotes lengthy growth of GAP43+ RGC axons. By contrast, i.o. lipopolysaccharide (LPS) injection causes an inflammatory response that is neurotoxic and does not support axon regeneration. The pro-regenerative effects of the immune system extend beyond the visual system; conditioning injury induced regeneration of ascending sensory axons in the spinal cord depends on a well-orchestrated inflammatory response.
We previously showed that β-glucan is the main active ingredient of zymosan and signals in a

dectin-1 and toll-like receptor 2 (TLR2) dependent manner to promote RGC axon regeneration. Dectin-1 is broadly expressed by innate immune cells, including microglia. Dectin-1 is absent from retinal neurons and astrocytes. To explore the contribution of microglia to zymosan mediated RGC protection and axon regeneration, we used pharmacological inhibition of Colony-Stimulating-Factor 1 receptor (CSF1R). Flow cytometry revealed a greater than 90% depletion of microglia in the retina, brain, and spinal cord in mice treated with inhibitor. Pharmacological inhibition of CSF1R does not alter ocular infiltration of blood-derived immune cells following i.o. zymosan injection. However, zymosan-mediated protection and regeneration of RGCs is partially, yet significantly reduced, indicating that microglia are important for the full-blown regenerative response to zymosan. Injury to the sciatic nerve, prior to transection of the dorsal columns (DC) in the spinal cord, results in enhanced (DC) axon regeneration. Pharmacological inhibition of CSF1R attenuates conditioning injury induced DC axon regeneration. Together, our studies reveal pro-regenerative effects of microglia in immune-mediated neuro-repair.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.20/G37

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: NIH Grant SC1GM095426

Title: Defective microglia-neuronal communication in mice expressing the human polymorphic variant CX3CR1$^{I249\text{-}M280}$ leads to the dysregulation of genes governing neurogenesis, myelination and microglial activation

Authors: *K. A. CHURCH[1], A. MENDIOLA[2], S. CARDONA[1], D. VANEGAS[1], S. LIRA[3], C.-H. LIN[1], A. E. CARDONA[4];
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Abstract: Multiple sclerosis (MS), a disease affecting 2.3 million people worldwide is characterized by the demyelination of axonal nerve fibers in the central nervous system (CNS) leading to disability and cognitive deficits. In the CNS, the CX3CR1 receptor is found on microglia and signals through the neuronal derived Fractalkine (FKN). This binding is known to inhibit microglia mediated neurotoxicity. Elucidating how human CX3CR1 polymorphisms

regulate microglia-neuronal function is relevant to understand mechanisms that lead to disease progression and to develop targeted neuroprotective approaches. To test the hypothesis that mice expressing the human CX3CR1$^{I249/M280}$ (hCX3CR1$^{I249/M280}$) polymorphic variant confer susceptibility to demyelination via microglial toxicity we utilized the cuprizone model of demyelination/remyelination. Our findings show severe demyelination, neuronal damage, and delayed remyelination, accompanied by microglia clustering in demyelinated regions of the corpus callosum (CC) in hCX3CR1$^{I249/M280}$mice. These findings were also confirmed in mice lacking the mouse receptor or the ligand FKN. Observing the loss of CC1^{+} mature oligodendrocytes in hCX3CR1$^{I249/M280}$ mice prompted the comparison of glial and neural progenitors indicating that CX3CR1-FKN may regulate neurogenesis thus interfering with neuron-OPC communication for oligodendrogenesis. NanoString analysis on tissues isolated from the SGZ neurogenic niche revealed an upregulation of genes involved in oxidative stress to neurons, notch signaling by microglia, and carbohydrate catalysis in hCX3CR1$^{I249/M280}$ expressing mice. The analysis also revealed a downregulation in genes involved in stem cell proliferation and differentiation in hCX3CR1$^{I249/M280}$ expressing mice. Overall our study indicates that FKN promotes neuroprotection by triggering anti-inflammatory microglial responses that support neurogenesis that are regulated by CX3CR1 polymorphic variants. This research has the potential to provide gene target therapies for the advancement of the MS field by providing evidence of a neuroprotective role of CX3CR1 that can be manipulated to enhance remyelination and repair.

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Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.21/G38

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: START grant 111/17, RWTH Aachen, P. Habib

Title: Microglial specific depletion of TAK1 contributes to neuroprotection after murine cerebral ischemia

Authors: *P. HABIB, T. ZEYEN, A. REICH, J. B. SCHULZ;
Dept. of Neurol., Univ. Hosp. Aachen, RWTH Aachen Univ., Aachen, Germany

Abstract: Background: Neuroinflammation and apoptosis play a crucial role in the expansion of the infarct core and the adjacent penumbra after cerebral ischemia. The key regulator of gene transcription NF-kB and the MAP kinases JNK, p38/MAPK and ERK share a common upstream

activator, the transforming growth factor-beta-activated kinase 1 (TAK1). TAK1 is upregulated after stroke and seems to have cell specific response pattern. Microglia are a main source of TAK1. However, little is known about the function and regulation of microglial-specific TAK1 after cerebral ischemia. **Purpose:**To gain further information about the biological function and regulation of TAK1 in microglial cells after cerebral ischemia.**Methods:**Tamoxifen-dependent conditional depletion of TAK1 in microglial cells was induced in CX3CR1-Cre^{ER}-TAK$^{fl/fl}$mice. The Cre negative CX3CR1-TAK$^{fl/fl}$mice served as a control group. We performed 30 minutes of middle cerebral artery occlusion (MCAo) followed by 72h of reperfusion.Laser Doppler flowmetry during surgery confirmed sufficient MCA occlusion.Weight, general status and focal neurologic dysfunction were evaluated at various time-points before and after MCAo or sham surgery. Lesion sizes weredetermined via computer-assisted infarct volumetry.Examining cell specific interactions primary microglia and mixed cell cultures were subjected tooxygen-glucose deprivation (OGD) followed by viability assays (LDH, CTB), gene expression analysis and protein measurement. TAK1-deficiency was induced by using tamoxifen and/or the general TAK1-inhibtor 5-7-Oxozeanol. **Results**: Infarctvolumes were reduced in TAK-1 deficient mice compared to the control group. In addition, TAK1-depletion significantly reduced neurological deficits and weight loss after MCAo. Ischemic tolerance of TAK1-depleted microglia as well as TAK-1 inhibited mixed cell cultures was significantly increased compared to the control group. Furthermore, TAK1-depletion and -inhibition decreased the mRNA- and protein-levels of pro-inflammatory cytokines, such as TNF-a, IL-1b and IL-6.**Conclusion:**Microglial-specific depletion/inhibition of TAK1offers a promising strategy in stroke therapy.

Disclosures: P. Habib: None. **T. Zeyen:** None. **A. Reich:** None. **J.B. Schulz:** None.

Poster

477. Neurotoxicity, Inflammation, and Neuroprotection: Microglia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 477.22/G39

Topic: C.07. Neurotoxicity/ Inflammation/ and Neuroprotection

Support: Leblang Charitable Foundation

Title: Increased phagocytic activity of monocyte derived microglia-like cells in adrenoleukodystrophy associated with neuronal damage

Authors: *Y. GONG[1], V. KREOUZIS[2], F. EICHLER[3];
[1]Massachusetts Gen. Hosp., Boston, MA; [2]MGH, Boston, MA; [3]Massachusetts Gen. Hosp. | Harvard Med. Sch., Boston, MA

Abstract: Adrenoleukodystrophy (ALD) and adrenal myeloneuropathy (AMN) are metabolic diseases associated with a deficiency in the ABCD1 peroxisomal transporter, leading to

ineffective metabolism of very-long chain fatty acids (VLCFA). Both have been associated with progressive myelin loss at their respective critical periods, but the presence and potential for neuronal damage has not been extensively studied. It has been previously shown that microglia activation is related to disease progression and symptomatology, while in addition peripheral blood monocytes infiltrate the brain through the blood brain barrier, thus being able to promote neuronal damage. We hypothesized that neuronal damage is thus in part associated with the microglia and peripheral blood monocyte infiltration of brain tissue in ALD and AMN, which would be associated with neuronal damage markers in patient sera. There was a around 50% increase in neurofilament light chain detected in serum of attempts with ALD and AMN (male: 176pg/ml±35, female: 176pg/ml±29) compared to controls (male: 90pg/ml±22, female: 126pg/ml±42), suggesting neuronal cell death in the central nervous system. To investigate the role of the immune driver in the brain of affected individuals we sought to derive microglia-like cells from patient peripheral blood monocytes. Preliminary data suggested a correlation between C1q and TNF-a with the phagocytic activity of the derived microglia-like cells towards synaptosomes in a small ALD and AMN cohort. The current work will further investigate the role of pro-inflammatory, anti-inflammatory, and phagocytic markers during a phagocytic event in the patient derived microglia-like cells. For conclusion: our finding of elevated neurofilament light chain suggests that axonal degeneration can be detected through a serum biomarker. The concurrent detection of activated monocytes suggests that increased phagocytosis may be contributing to axonal degeneration in humans affected by AMN. Importantly our findings in combined biomarkers of monocyte and axonal dysfunction allow for more effective temporal diagnosis of pathology associated with ABCD1 peroxisomal deficiency.

Disclosures: Y. Gong: None. **V. Kreouzis:** None. **F. Eichler:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.01/G40

Topic: C.09.Stroke

Support: R15 HD093086
National Science Foundation under an Individual Research and Development plan
Erasmus+ KA 107 action (USA-ITALY)

Title: The utility of vibrotactile cues as supplemental movement feedback varies across application site and individuals after stroke: A pilot study

Authors: *A. THOMAS[1], V. A. SHAH[1], G. BALLARDINI[2], T. STOECKMANN[3], M. CASADIO[2], J. R. MCGUIRE[4], R. A. SCHEIDT[1,5,6], L. A. MROTEK[1];
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Genova, Genova, Italy; [3]Physical Therapy, Marquette Univ., Milwaukee, WI; [4]Physical Med. and Rehabil., Med. Col. of Wisconsin, Milwaukee, WI; [5]Feinberg Sch. of Medicine, Northwestern Univ., Chicago, IL; [6]Div. of Civil, Mechanical and Manufacturing Innovations, Natl. Sci. Fndn., Alexandria, VA

Abstract: Vibrotactile feedback (VTF) can provide a form of supplemental movement feedback that improves upper extremity movement accuracy in the absence of visual feedback in healthy individuals. A recent pilot study suggests that VTF can also improve motor control in the more involved arm in some survivors of stroke by providing cues about that limb's motion. We sought to advance development of a new VTF-based assistive technology by determining if there is a single best site on the body to apply VTF, one that is common across individuals. Four stroke survivors used VTF to guide 1D (left/right) reaching movements. VTF was provided using two 10 mm eccentric rotating mass vibration motors taped to specific locations on the body. The motors have an operating range of 50-250 Hz and a peak vibration of 2.8 G; vibration was described as mild to moderate. Participants sat comfortably with their more-affected hand fixed to the handle of a passive 2D horizontal planar robot and were asked to make reaches with that hand. They saw a 5x5 grid of points (the *workspace*) on a vertically oriented screen with the five points of the middle row used as targets. A single point was highlighted when it was the current target. VTF encoded the position of the reaching hand; no vibration was applied when the hand was at the center of the workspace and vibration intensity increased as the hand moved away from the center of the workspace. Trials consisted of 16 reaches between the 5 points in the middle row of the grid. Subjects verbally indicated when each target was acquired. Subjects experienced eight feedback conditions: visual cursor feedback of hand motion; no vision & no VTF. VTF was applied to each forearm (motors on C6/C8 dermatomes on the wrist extensor muscles); near each knee (motors on L3/L4 dermatomes on the knee extensor muscles); and torso (motors on C6 dermatome on the trapezius muscle). We computed the target capture error at the end of each reach. Performance excelled with visual feedback in all subjects. Ability to interpret and use VTF varied widely across application sites in a way that varied person by person. Two of the participants capitalized on the VTF to improve reach accuracy in the absence of visual feedback relative to the no vision & no VTF condition. One of these individuals performed best when the VTF was applied to the less-affected knee, whereas the other successfully used VTF when it was applied to the less-affected arm. For the other two participants, performance degraded in the presence of VTF. These data, collected in a small heterogenous cohort, suggest that an individualized approach may be needed when developing VTF-based assistive technologies to augment upper extremity kinematic performance.

Disclosures: A. Thomas: None. **V.A. Shah:** None. **G. Ballardini:** None. **T. Stoeckmann:** None. **M. Casadio:** None. **J.R. McGuire:** None. **R.A. Scheidt:** None. **L.A. Mrotek:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.02/G41

Topic: C.09.Stroke

Support: Shared Equipment Evaluation Program, Department of Veterans Affairs (BX-17-015)
Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N2864C)
Office of Research and Development, Rehabilitation R&D Service, Department of Veterans Affairs (N9288C)
NIH NINDS (U01NS098968)
MGH-Deane Institute
The Executive Committee on Research (ECOR) of Massachusetts General Hospital
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: Theta power is a longitudinal EEG spatial and spectral biomarker of spontaneous motor recovery after stroke

Authors: *L. M. OSTROWSKI[1,2], A. N. DUSANG[4,5,1], A. CLOUTIER[2], F. GIATSIDIS[2], S. S. CASH[3,6], L. R. HOCHBERG[1,4,2,6,5], D. J. LIN[2,1];
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Abstract: INTRODUCTION: Current neurorestorative therapy options to enhance upper extremity motor recovery after stroke are limited. Neurological biomarkers that reflect underlying biological processes and correlate with motor recovery could provide important surrogate clinical endpoints for stroke recovery trials. Slow-wave oscillations on EEG have been linked to cerebral dysfunction after stroke, but robust EEG biomarkers that track with upper extremity motor recovery have yet to be defined. Here, our aim is to define spatial and spectral properties of EEG that provide optimal biomarkers for upper extremity motor recovery in the first three months after stroke.
METHODS: We recorded natural-state, high-density 128-channel EEG data in 15 patients within one week and subsequently at six weeks and three months after ischemic stroke. We used a

customized semi-automated pipeline for offline EEG data pre-processing (eye-blink and artifact rejection). Spectral power was calculated in leads overlying the contra- and ipsilesional motor cortex, contra- and ipsilesional hemispheres, and over the whole scalp, in predefined bands: delta (1-4 Hz), theta (5-7 Hz), alpha (8-12 Hz) and beta (13-30 Hz). We used the Upper Extremity Fugl-Meyer Assessment (UE-FMA) to quantify upper limb motor impairment at each time point.
RESULTS: Absolute theta power was the only spectral feature which correlated with UE-FMA at all timepoints (at enrollment $R^2 = 0.23$, $p = 0.067$; at six weeks $R^2 = 0.35$, $p = 0.026$; at three months $R^2 = 0.25$, $p = 0.067$, Pearson's r). The largest number of spectral correlates were found at six weeks, where relative theta power in the lesioned hemisphere had the strongest relationship of all spectral bands in all spatial regions ($R^2 = 0.63$, $p < 0.001$). Favorable change in UE-FMA linearly correlated with decrease in absolute theta power in the lesioned hemisphere between six weeks and three months ($R^2 = 0.34$, $p = 0.028$), but not between enrollment and six weeks. Finally, theta power in the lesioned hemisphere at six weeks, but not at enrollment, was predictive of UE-FMA outcome at three months (absolute power $R^2 = 0.25$, $p = 0.066$; relative power $R^2 = 0.54$, $p = 0.003$).
CONCLUSION: EEG spatial and spectral features contain useful information indicative of spontaneous upper extremity motor recovery. Theta power in the lesioned hemisphere may be an optimal cross-sectional and longitudinal spectral biomarker and may be particularly informative for motor recovery at six weeks post-stroke as opposed to the immediately acute setting.

Disclosures: L.M. Ostrowski: None. **A.N. Dusang:** None. **A. Cloutier:** None. **F. Giatsidis:** None. **S.S. Cash:** None. **L.R. Hochberg:** None. **D.J. Lin:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.03/G42

Topic: C.09.Stroke

Support: FAPESP: 2016/21470-3

Title: Cell therapy evaluation using the triple model image of stem cell labeled with multimodal nanoparticle in type two diabetic rats with stroke

Authors: M. P. NUCCI[1,2], J. V. M. FERREIRA[1], P. C. MACHADO[1], J. B. MAMANI[1], Y. O. PINTO[1], H. R. DA SILVA[1], F. A. DE OLIVEIRA[1], G. N. A. REGO[1], I. S. FILGUEIRAS[1,3], P. D. ESPINHA[1], L. E. B. DE SOUZA[4], D. M. C. FANTACINI[4], A. T. KONDO[1], D. T. COVAS[4], ***L. F. GAMARRA**[1];
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Abstract: The objective of this work was to evaluate cell therapy in type two diabetic rats with stroke using the triple model image of stem cell labeled with multimodal nanoparticle. After the isolation, immunophenotypic characterization and lentiviral transduction of human bone marrow stem cells (hBM-MSC), these cells were labeled with multimodal nanoparticles (MNP) with magnetic and fluorescent properties (visible and infrared wavelength) that were previously characterized. Cell viability was analyzed by MTT assay and BLI, and quantify the MNP load internalized into the cells by MRI, NIRF, and ICP-MS. Male Wistar rats (200-230g) were divided into four groups: non-diabetic and diabetic, followed stroke induction or sham surgery. The type 2 diabetes animals fed high-fat diet for one week, followed by a one-time injection of 30 mg/kg streptozotocin. The stroke induction was performed using photothrombosis in the motor cortex, confirming the ischemic lesion by local blood perfusion analysis and TTC staining. 24h after surgery, half of the animals of each group received hBM-MSC labeled with MNP. The triple modal image (MRI, NIRF and BLI) was performed before surgery and 4, 24h and 7 days after cells implantation. Also, cell therapy was evaluated using behavioral tests and immunohistochemical staining. Immunophenotypic characterization and differentiation induction of hBM-MSC showed to be adequate for cell therapy. Physicochemical characteristics of the MNP was an average diameter of 40.1 nm and zeta potential of 32.0 mV in pH of 7.4. The optical characterizations showed the dual fluorescence (visible and infrared). The signal of MNP load internalization in hBM-MSC had a close correlation (r=0.99) with the corresponding MNP-labeled by MRI, ICP-MS and NIRF, in which the maximum value of MNP load found was 0.65 *p*g of MNP/cell with a cellular viability reduction of less than 8%. After 7 days of hBM-MSC implantation, the behavior analysis showed high improvement in T2MD+Stroke in comparison to sham and stroke groups ($p<0.001$), as well as T2MD group($p=0.05$), as well as the BLI signal of the T2MD+Stroke group (3E9 photons/s) showed high value in comparison to stroke group (5E8 photons/s), without signal detection in T2MD and sham groups, while the NIRF and MRI analysis showed low signal in all groups. The Fluoro-Jade B identified neuronal degeneration secondary to ischemia and NeuN showed the density neuronal after cells implantation, in according to behavioral pattern of recover. This study showed functional and structural improvement after cell therapy in stroke lesion of diabetic rats using nanobiotechnological resources.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.04/G43

Topic: C.09.Stroke

Support: Department of Anesthesiology
NIH Grant NS099590

Title: Chemogenetics-mediated acute inhibition of excitatory neuronal activity improves stroke outcome

Authors: Y.-C. WANG[1], F. GALEFFI[2], W. WANG[1], X. LI[1], H. SHENG[1], U. HOFFMANN[1], D. A. TURNER[2], ***W. YANG**[1];
[1]Anesthesiol., [2]Neurosurg., Duke Univ. Med. Ctr., Durham, NC

Abstract: Introduction. Ischemic stroke is a devastating disease caused by a sudden interruption of blood flow to an area of the brain and subsequent brain infarction. Immediately after ischemic stroke and during infarct maturation, a cascade of deleterious events takes place, including metabolic supply-demand mismatch, dysfunction in ion channels, and excessive release of neurotransmitters. Accordingly, homeostasis in neuronal networks is impaired, which leads to excitotoxicity and peri-infarct depolarizations, both crucially contributing to infarct expansion. In the current study, we hypothesized that inhibition of excitability and depolarization of excitatory neurons in the brain reduces the occurrence of cortical spreading depolarizations and improves stroke outcome. To test this hypothesis, we used a chemogenetic approach that is based on Designer Receptors Exclusively Activated by Designer Drugs (DREADDs).
Methods. We generated hM4Di-TG transgenic mice expressing the inhibitory hM4Di, an DREADD receptor, in forebrain excitatory neurons. Clozapine-N-oxide (CNO) was used to activate hM4Di DREADD. Electrophysiological analysis of excitatory neuronal suppression in the hM4Di-TG mouse brain was conducted both in hippocampal slices by synaptic responses and in vivo with induction of potassium-evoked cortical spreading depression occurrence. Ischemic stroke was induced by transient occlusion of the middle cerebral artery. Neurologic function and infarct volumes were evaluated.
Results. Activation of the inhibitory hM4Di DREADD by CNO led to a significant reduction in evoked synaptic responses in hippocampal slices. Likewise, potassium-induced cortical spreading depression episodes were diffusely inhibited, including frequency, latency to onset, and DC shift duration. With respect to physiology and motor function, hM4Di expression showed no overt effect in the absence of CNO, and CNO treatment alone did not induce any notable changes in control or hM4Di-TG mice. Finally, hM4Di-TG mice treated with CNO at either before ischemia or after reperfusion exhibited significantly improved neurologic function and smaller infarct volumes compared to CNO-treated control mice.
Conclusions. Our data indicate that acute inhibition of a subset of excitatory neurons after ischemic stroke can prevent brain injury and improve functional outcome. This study, together with the previous work in optogenetic neuronal modulation during the chronic phase of stroke, supports the notion that targeting neuronal activity is a promising strategy in stroke therapy.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.05/G44

Topic: C.09.Stroke

Support: MicroTransponders, Inc.

Title: Gait endurance improves after vagus nerve stimulation combined with upper limb rehabilitation in ischemic chronic stroke, a case series

Authors: *A. VAN DE WINCKEL[1], S. GONZALES[2], D. K. KLINE[3], C. N. PRUDENTE[4], T. BISSON[2], K. L. FROST[5], D. PIERCE[4], B. TARVER[4], N. D. ENGINEER[4], T. J. KIMBERLEY[3]; [1]Dept. of Rehab Medicine, Div. of Physical Therapy, Div. of Rehabil. Sci., [2]Dept. of Rehabil. Medicine, Div. of Physical Therapy, Univ. of Minnesota Twin Cities, Minneapolis, MN; [3]Sch. of Hlth. and Rehabil. Sci., Massachusetts Gen. Hosp. Inst. for Hlth. Professions, Boston, MA; [4]MicroTransponder, Inc., Austin, TX; [5]Boston Scientific, St Paul, MN

Abstract: Introduction Recent studies demonstrated improved upper limb motor function by pairing vagus nerve stimulation (VNS) with upper limb motor rehabilitation in patients with chronic stroke. The goal of this case series study was to determine whether VNS/upper limb rehabilitation generalized to improved walking ability without specific gait training. **Methods** Six participants (3 female) with unilateral ischemic chronic stroke were randomized in a double-blinded, sham-controlled pilot that was a subset of a larger study. The average age was 63.33 ± 8.00 years (53-73 years), 5 left and 1 right hemiplegia; 18.00 ± 6.07 months post-stroke. All participants had left VNS implantation. The experimental group received 0.8 mA VNS stimulation with upper limb rehabilitation, 3x/week for 6 weeks (18 visits) involving more than 400 movement trials. The control group received the same rehabilitation but with sham-VNS (0.0mA). Participants, assessors and therapists were blinded to group allocation during the real-VNS versus sham-VNS treatment period. After 3 months, group allocation was revealed and the control group crossed-over to receive 6 weeks of 0.8mA VNS paired with rehabilitation. All patients received VNS combined with home-based upper limb rehabilitation in the follow-up period. Outcomes included 6 Minute Walk Test (6MWT), self-paced and fast-paced 10m walk test at baseline, post-test (6 weeks) and follow up assessments. **Results** For the 6MWT, the experimental group improved by 32.97 ± 20.63m at post-test, 39.72 ± 22.59m at 3 months and 31.92 ± 22.01m at 2 years follow-up compared to baseline. Two of three participants in the experimental group exceeded minimal clinical important difference (36.6m) in walking distance. While initial improvement of 8.89 ± 13.67m was seen post-training in the sham-VNS group, the group decreased -44.86 ± 24.67m walking distance at 3 months from baseline. They improved 44.1 ± 15.61m after 0.8mA VNS/rehabilitation and 48.86 ± 17.52m at 3 months, but declined -

16.48 ± 25.19m walking distance at 2 years follow-up, all compared to the original baseline. However, the control group practiced less at home (270.67 ± 50.62 sessions) compared to the experimental group (982.00 ± 307.44 sessions). Self-paced and fast-paced walking speed did not change appreciably during treatment in either group. **Conclusions** Gait endurance improved after VNS/upper limb training compared to sham-VNS/upper limb rehabilitation, even though there was no statistical significance given the small sample sizes. Gait speed does not appear to be impacted by VNS. This preliminary evidence suggests secondary gains following VNS may generalize beyond the trained activities.

Disclosures: **A. Van de Winckel:** A. Employment/Salary (full or part-time):; AVDW was paid part-time as PI on the mentioned grant (PI AVDW; co-PI TJK), MicroTransponder, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; AVDW is PI on clinical trial (MicroTransponder, Inc. had no responsibility for analysis/interpretation of data, or for writing/submitting abstract.), MicroTransponder, Inc.'s Vivistim System. **S. Gonzales:** A. Employment/Salary (full or part-time):; SG was paid part-time as study staff on the mentioned grant (PI AVDW; co-PI TJK), MicroTransponder, Inc. **D.K. Kline:** A. Employment/Salary (full or part-time):; DK was paid part-time as study staff on the mentioned grant (PI AVDW; co-PI TJK), MicroTransponder, Inc. **C.N. Prudente:** A. Employment/Salary (full or part-time):; employee, MicroTransponder, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, MicroTransponder, Inc. **T. Bisson:** A. Employment/Salary (full or part-time):; TB was paid part-time as study staff on the mentioned grant (PI AVDW; co-PI TJK), MicroTransponder, Inc. **K.L. Frost:** A. Employment/Salary (full or part-time):; KF was paid part-time as study staff on the mentioned grant (PI AVDW; co-PI TJK), MicroTransponder, Inc. **D. Pierce:** A. Employment/Salary (full or part-time):; employee, MicroTransponder, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, MicroTransponder, Inc. **B. Tarver:** A. Employment/Salary (full or part-time):; employee, MicroTransponder, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, MicroTransponder, Inc. **N.D. Engineer:** A. Employment/Salary (full or part-time):; employee, MicroTransponder, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); stock options, MicroTransponder, Inc. **T.J. Kimberley:** A. Employment/Salary (full or part-time):; TJK was paid part-time as co-PI on the mentioned grant (PI AVDW; co-PI TJK), MicroTransponder, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; TJK is co-PI on clinical trial (MicroTransponder, Inc. had no responsibility for analysis/interpretation of data, or for writing/submitting abstract.), MicroTransponder, Inc.'s Vivistim System.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.06/H1

Topic: C.09.Stroke

Title: Effect of EMG triggered electrical stimulation with blood flow restriction technique on hand function in stroke survivors - A randomized controlled study

Authors: *N. CHOUDHARY;
Physiotherapy and Rehabil., Government Physiotherapy Col. (Dr. S.N. Med. College), Jodhpur, India

Abstract: Background and Aims: Post stroke upper limb impairment strongly influences disability and patient's quality of life. Blood flow restricted (BFR) exercise has been identified as a possible rehabilitation intervention. The objective of this study was to determine the effectiveness of electromyogram (EMG) triggered neuromuscular electrical stimulation (NMES) combined with BFR to improve arm strength and function in stroke survivors. **Methods:** 6 chronic stroke survivors were screened and randomized into experimental and control groups with n=3 each. Control group received standard upper limb rehabilitation intervention along with EMG triggered NMES to wrist extensors for 15 minutes once daily, 4 days a week for 10 weeks. Along with the standard interventions, subjects in the experimental group were given EMG triggered NMES to wrist extensors combined with BFR for 10 minutes (fig.1). Vascular occlusion was achieved using elastic wraps proximally on the arm just below the shoulder joint. The Fugl-Meyer (FM) motor assessment for upper extremity was the primary outcome measure. Motricity Index (MI), Box and Block test (BBT) and Barthel Index (BI) were secondary outcome measures. Clinical assessment was taken at baseline, after 5th week and at the end of 10th week. **Results:** Statistical analysis was conducted using SPSS 22. Scores of four outcome measure (FM, MI, BBT and BI) were compared using ANOVA and it was observed that there was a highly significant difference ($p > 0.01$) between these outcome measures. Further analysis in the scores of FM ($F= 12.067$), BBT ($F= 10.035$) and BI ($F= 7.538$) showed significant difference ($p > 0.01$) between control and experimental group whereas difference in MI scores were non-significant. **Conclusions:** EMG triggered neuromuscular electrical stimulation combined with BFR is a safe and feasible strategy for stroke rehabilitation to strengthen upper limb without using external weights.

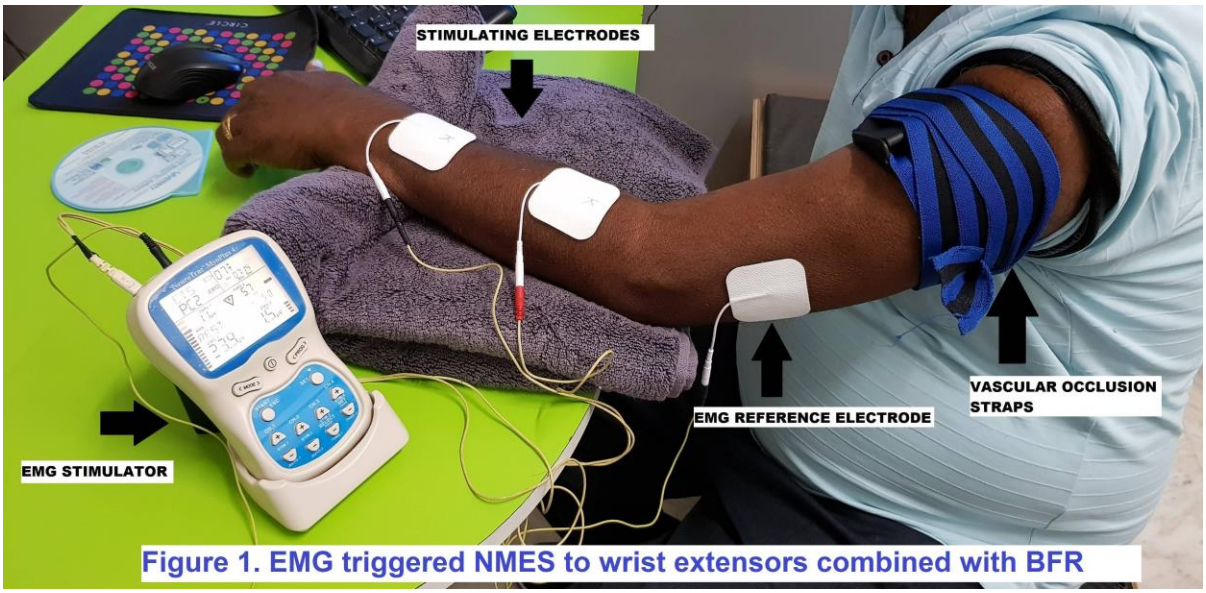

Figure 1. EMG triggered NMES to wrist extensors combined with BFR

Disclosures: **N. Choudhary:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.07/H2

Topic: C.09.Stroke

Support: the Kamonovitz Center for CNS Repair
the Office of Academic Affiliations VA Advanced Fellowship in Polytrauma/Traumatic Brain Injury Rehabilitation
Department of Veterans Affairs

Title: Improving recovery after ischemic stroke using a neuromuscular stimulation method-A rodent model

Authors: ***S.-Y. TSAI**[1], J. Y. WU[1], J. S. WU[1], R. C. HOFLER[2], V. HUSAK[1], S. T. TON[1], J. S. WALTER[1], G. L. KARTJE[1], R. P. NOCKELS[2];
[1]Res. Service, Edward Hines Junior VA Hosp., Hines, IL; [2]Neurolog. Surgery, Loyola Univ. Med. Ctr., Maywod, IL

Abstract: Lack of blood flow to the brain, i.e., ischemic stroke, results in loss of nerve cells and therefore loss of function in the affected brain regions. There is no effective treatment to improve

lost function except restoring blood flow within the first several hours. The purpose of this work was to examine the use of electrical stimulation on the impaired upper extremity to improve functional recovery after stroke. We developed an animal model using implanted electrodes onto the nerve of the paretic limb and applied daily electrical stimulation. The skilled forelimb reaching test and ladder rung bar walk test were used to evaluate functional outcome after stroke and electrical stimulation. We also used anterograde tracing from the layer V pyramidal neurons to evaluate possible formation of new neuronal connections from the contralesional cortex to the deafferented subcortical structures, such as the red nucleus, pons, and spinal cord. Our preliminary results indicate that our model of peripheral nerve electrical stimulation promotes recovery after stroke. The mechanisms underlying this recovery are presently under investigation.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.08/H3

Topic: C.09.Stroke

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Title: Serum BDNF levels by BDNF genotype in stroke patients

Authors: *W. CHANG, K. KIM, A. LEE, H. KIM, Y.-H. KIM;
Physical and Rehabil. Med., Samsung Med. Center, Sungkyunkwan Univ. Sch. of Med., Seoul, Korea, Republic of

Abstract: Introduction: Brain-derived neurotrophic factor (BDNF) is involved in neuronal survival, synaptic plasticity, learning and memory, and neuroplasticity in both the intact and the damaged brain. A single nucleotide polymorphism in the human BDNF gene at codon 66 (val66met) is present in one or both alleles. The replacement of val66 by met66 disrupts cellular processing, trafficking, and activity-dependent secretion of BDNF. However, there was a lack of study with serum BDNF according to BDNF genotype in stroke patients. In this study, we aimed to investigate the difference of serum BDNF level according to BDNF genotype in subacute stroke patients. **Methods:** Ninety-two stroke patients (mean age 63.1 yrs) were recruited in this study. All participants took the standard rehabilitation program included daily 2-hours of

physical therapy and 1-hour of occupational therapy, 5 days a week, for 2 weeks during subacute stroke phase (from 2 weeks after onset). We measured the serum BDNF, proBDNF and MMP-9 at T0 (before the standard rehabilitation program), and T1 (2 weeks after the standard rehabilitation program). In addition, all participants were assessed with NIH Stroke Scale (NIHSS) for stroke severity, Fugl-Meyer assessment (FMA) for motor function and for Korean Mini-Mental State Examination (K-MMSE) for cognitive function at T0 and T1. Data were analyzed by the BDNF polymorphism (Val/Val group vs. Met allele group). **Results:** 46.4% and 53.6% participants were classified into Val/Val and Met allele groups. Each stroke severity, motor and cognitive function showed significantly improvement after the standard rehabilitation program for 2 weeks in each group ($p<0.05$). There was no significant difference in serum BDNF at T0 between the two groups; however, proBDNF showed significant higher in Met allele group than Val/Val group ($p<0.05$). In Val/Val group, there was no significant difference in serum BDNF between T0 and T1. However, serum BDNF and proBDNF showed the increases from T0 to T1 in Met allele group, respectively ($p<0.05$). **Conclusion:** These results demonstrated that the polymorphism of BDNF may influence on the serum BDNF and proBDNF levels by the comprehensive rehabilitation in subacute stroke patients. Further study will be needed to clarify the role of serum BDNF in subacute stroke patients.

Disclosures: W. Chang: None. **K. Kim:** None. **A. Lee:** None. **H. Kim:** None. **Y. Kim:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

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Program #/Poster #: 478.09/H4

Topic: C.09.Stroke

Support: Max Planck Society

Title: Augmented-reality-based paretic arm training improves reaching performance by altering functional brain networks in chronic stroke

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Abstract: Stroke-induced persistent arm paresis, and its detrimental consequences on life quality is a major challenge for neurorehabilitation research. Here we assessed behavioral and neuronal effects of an augmented-reality (AR)-based paretic arm training that aims to enhance task-specific function while preventing compensatory movements. Nineteen chronic stroke patients (age: 60.4±13.7 years, onset time 6.4±4.7 years ago) underwent an object-hit training in the AR environment using the exoskeleton system KINARM (BKIN Technologies Ltd, Ontario,

Canada). This device creates a well-controlled environment for movement training and assessment while restricting trunk compensation. The whole experiment lasted 8 weeks, with a four-week control period (only regular therapy), a four-week training period (AR-paretic arm training and regular therapy), and three measurement points (baseline, pre-training, and post-training). The training comprised twelve sessions (40 minutes/day, three days/week). At each measurement points, patients performed: (1) behavioral assessments, including daily activity tasks (Jebsen-Taylor Hand Function Test; JTHF) and basic reaching kinematic assessment (Visually-Guided Reaching test; VGR inside the KINARM); (2) MRI, including resting-state fMRI, elbow movement task-fMRI and structural scans. While no changes were found for the control period (pre-training vs. baseline), our training induced significant changes (post-training vs. pre-training) on behavior and functional MRI. Behaviorally, we found that patients did not only complete daily activity tasks more efficiently (completion time: from 355.44±67.36 sec to 340.30±66.32 sec, $p<0.001$), but also improved the trajectory accuracy during the basic reaching task (trajectory deviation: from 1.38±0.10 cm to 1.23±0.03 cm, $p<0.01$). Task-fMRI during paretic elbow movements revealed a reduction in BOLD signal in the anterior cingulate cortex (cluster corrected $p<0.05$) after training, a region related to error monitoring. Our findings demonstrate that a short-term augmented-reality-based paretic arm training induces brain plastic changes and further improve daily living activity in chronic stroke.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

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Topic: C.09.Stroke

Support: NIH Grant R01NS069726
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Title: Role of astrocyte-derived GDNF in neuronal protection and brain recovery after ischemic stroke

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Abstract: Astrocytes play a non-cell autonomous role in neuroprotection after ischemic stroke. Glial cell-derived neurotrophic factor (GDNF) was originally isolated from a rat glioma cell-line supernatant and is a potent survival neurotrophic factor. Focal ischemic stroke (FIS) is a leading cause of human death. Reactive gliosis and glial scar formation is a hallmark of FIS. Reactive

astrocytes experience dramatic spatial and temporal changes of morphology and gene expression in peri-infarct region (PIR). Here, we investigated whether and how reactive astrocytes-derived GDNF affects neuronal death and brain damage after FIS. Using *CreER^{T2}-LoxP* recombination technology, we generated inducible and astrocyte-specific Gdnf conditional knockout (cKO), i.e., *Glast-Gdnf$^{-/-}$* cKO mice to investigate the effect of endogenous astrocytic GDNF on neuronal death, brain damage, and recovery after photothrombosis (PT)-induced FIS. Under non-ischemic conditions, we found that *Glast-Gdnf$^{-/-}$* cKO mice exhibited significant lower number of Brdu+ and Ki67 cells as well as DCX+ cells in the dentate gyrus (DG) in hippocampus in adult mice, indicating astrocytic GDNF can promote adult neurogenesis. Under ischemic conditions, *Glast-Gdnf$^{-/-}$* cKO mice had a significant reduction in infarct volume after 2, 4 and 14 days after PT as compared with WT litter mates after PT. *Glast-Gdnf$^{-/-}$* cKO mice also exhibited a significant reduction in FJB+ degenerating neurons in PIR. Moreover, *Glast-Gdnf$^{-/-}$* cKO mice had lower densities of Brdu+ and Ki67+ cell in the PIR than WT mice, indicating that astrocytic GDNF can promote cell proliferation in the PIR. Furthermore, behavioral tests showed that deletion of GDNF caused more motor deficits after stroke and low recovery. In summary, our study suggests that reactive astrocytes-derived GDNF plays important roles in reducing neuronal death and brain damage through neural regeneration in PIR after PT, and promoting endogenous neurotrophic factor release from reactive astrocytes might be a potential therapeutic approach in stroke therapy.
Key words: Focal ischemic stroke; penumbra; neuronal death; brain infarct; astrocytes; Glast; PT; cKO mice

Disclosures: Z. Zhang: None. **N. Zhang:** None. **S. Ding:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.11/H6

Topic: C.09.Stroke

Support: FAPESP: 2016/21470-3

Title: Optimizing conditions for labeling bone marrow stem cell with multifunctional near-infrared dye-magnetic nanoparticles for cells homing and tracking analysis in global cerebral ischemic model

Authors: *M. P. NUCCI[1,2], I. S. FILGUEIRAS[2,3], J. V. M. FERREIRA[2], P. C. MACHADO[2], J. B. MAMANI[2], F. A. DE OLIVEIRA[2], G. N. A. REGO[2], P. ESPINHA[2], L. E. B. DE SOUZA[4], D. M. C. FANTACINI[4], A. T. KONDO[2], D. T. COVAS[4], L. F. GAMARRA[2];
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Abstract: Optimizing conditions for the labeling process in bone marrow stem cells (BMSC) was performed with different concentrations of multifunctional near-infrared dye-magnetic nanoparticles (MFNP): 10, 30 and 50 µgFe/mL, 10^6 cells/well were plated into 24 wells plate with 2mL of RPMI medium (10% SFB), in order to determine the best concentration in the internalization process. The process was performed in three magnetic conditions: without magnet, with static magnet (placed below the culture wells) and with dynamic magnet (oscillating in the frequency of 0.25Hz), with and without filtration (0.45µm filter), as also in different incubation times: 3, 6, 10, 18 and 24 hours. In each condition analyzed was evaluated the cellular viability by MTT and BLI assays. The quantification of MFNP internalized was analyzed by ICP-MS, near-infrared fluorescence (FLI) and MRI. After determining the best condition of the internalization of MFNP into BMSC, these cells were administered via tail in rats (N=20) with global cerebral ischemia (Pulsinelli et al., 1979), that is the permanent occlusion of bilateral vertebral arteries and temporary occlusion of bilateral common carotids arteries. The homing and tracking of MSC labeled with MFNP after implanted in the rats were evaluated by BLI, FLI, and MRI at 1, 3, 7 and 14 days. The best condition of the internalization of MFNP into BMSC was with the dynamic magnet (32,7ng/10^6cells) as showed by Prussian blue, ICP-MS and FLI, had a higher concentration in comparison with the static magnet with 10,3ng/10^6cells and without magnet 6,4ng/10^6cells. The best incubation time was with 10 hours, following this time was observed a plateau until 18 hours, finalized with an internalization decay, this fact can be explained considering the exocytosis process of the MFNP by BMSC. The cellular viability for all concentrations and incubation times was low than 9%. Using the best condition of MFNP labeling, after one day of cells implantation was possible to detect in the global cerebral ischemia model the BMSC homing and tracking by FLI (3,21x10^8 photons/s) and BLI (8,21x10^8 photons/s) and with lower sensitivity by MRI. After 7 days of cells implantation, the FLI signal was lower 3,4x10^7 photons/s, but the BLI signal increase to 3,4x10^9 photons/s. In the control animals were not possible to localize in the brain the BMSC labeled with MFNP. The ICP-MS quantification of *ex vivo* brain showed a MFNP load proportionate to found by FLI (1d: 8ng, 3d: 7.3, 7d: 3.2ng e 14d: 0.5ng). Therefore, the optimization of internalization parameters of the MFNP into stem cells is essential to analyze the cells homing and tracking for a long time during the cellular therapy process.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

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Topic: C.09.Stroke

Support: NIH Grant R01-NS076942-05 to CPC
NIH Grant R25-NS065723 to WAZ

Title: No evidence of functional peri-infarct circuit remapping in mouse somatosensory cortex after ischemic stroke

Authors: *W. ZEIGER[1], M. MAROSI[2], S. SAGGI[1], C. HE[1], C. PORTERA-CAILLIAU[1]; [1]Neurol., Univ. of California Los Angeles, Los Angeles, CA; [2]Femtonics, Budapest, Hungary

Abstract: Stroke is the fifth leading cause of death and the leading cause of adult disability in the United States. While advancements have been made in prevention and acute treatment of stroke, there is currently a paucity of treatments aimed at improving recovery. Many patients exhibit partial spontaneous recovery, suggesting that the brain has endogenous mechanisms to restore lost functions. The process by which one area of the brain subsumes the function previously performed by an area damaged by stroke is termed remapping. Strong evidence supports a role for peri-infarct cortex in remapping of function following stroke; this area undergoes structural, physiologic, and transcriptomic changes during recovery, but the downstream effects on cortical circuits are largely unknown. Here, we targeted photothrombotic (PT) strokes to individual barrels in the barrel field of mouse primary somatosensory cortex, sparing neighboring barrels. We hypothesized that spared barrels in the peri-infarct homotopic cortex would take over the 'lost' functionality by responding to the whisker. Initially, we used longitudinal intrinsic signal imaging (ISI) through chronically implanted cranial windows before and after a PT stroke to the C1 barrel but found no evidence of remapping (i.e., regions that responded to C1 whisker stimulation) anywhere in the peri-infarct region even up to one month after stroke. However, it is possible that the remapping process involved small numbers of neurons that would not evoke a sufficient signal to be detected by ISI. Therefore, we turned to *in vivo* two-photon (2P) calcium imaging in *Thy1*-GCaMP6s transgenic mice before and after a PT stroke to the C1 barrel to monitor whisker-evoked responses of individual layer 2 /3 neurons in the adjacent D3 barrel. At baseline (before stroke), ~25% of active neurons in the D3 barrel respond to stimulation of the D3 whisker, but only ~8% of neurons respond to the C1 whisker. Although we predicted that the percentage of C1 whisker-responsive neurons in the intact D3 barrel would increase after stroke, we found that only ~2% of neurons in the D3 barrel responded to C1 whisker stimulation, even at one month after stroke. These results suggest that the spared, peri-infarct homotopic barrel cortex is not involved in functional remapping after stroke, despite evidence of structural plasticity. We are presently testing whether additional factors that drive plasticity are required to recruit neurons in peri-infarct cortex in remapping lost functionalities. Our data implicates other mechanisms (e.g., subcortical) in functional recovery after stroke.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

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Topic: C.09.Stroke

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HI16C1012

Title: Effects of environmental enrichment on the expression of presynaptic active zone proteins in the brain of hypoxic-ischemic encephalopathy

Authors: *S.-Y. SONG[1,3,4], S. PYO[1,3,5], H.-S. OH[1], J. YU[1,3], Y.-K. SHIN[1,3], A. BAEK[2], J. SEO[1,3], S. WI[1,3], B.-G. NAM[1,3,4], E. CHO[1,3,5], S. JO[1,3,5], H. JEONGHYUN[1,3,4], J. CHOI[6], S.-R. CHO[1,3,4];
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Abstract: Hypoxic ischemic encephalopathy (HIE) is a disease of the brain caused by the lack of perfusion to the brain. The need for an effective treatment of ischemic brain disease is all the more increasing, but the current treatment fails to achieve full recovery and the mechanism of its recovery is not well understood.The brain is an organ that is capable of modify itself as a response to environmental stimuli. Environmental enrichment (EE), which consists of complex combinations of physical, cognitive, and social stimuli, is a therapeutic approach that employs this trait of plasticity.
However, not many are known about the changes in the expression protein molecules that EE can bring. Through this study, we focus on how EE can enhance synaptic plasticity in the protein level, and lean toward the specific mechanisms of how rehabilitation can affect synaptic plasticity.
At six weeks of age, the mice were randomly assigned to either EE or standard cages (SC) for two months.Rotarod, and ladder walking 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 cortex, basal ganglia and hippocampus. Among the synaptic plasticity-regulating genes, the expression of Active zone and Ca^{2+} channel proteins was also confirmed.The level of synaptic plasticity-regulating genes was significantly higher in the cortex, basal ganglia and hippocampus of EE mice at 8 weeks.
By exposing HIE models to EE, we seek to induce changes in the synaptic plasticity, and the

consequent changes in the expression of neurons, presynaptic active zone protein such as RIM, and behavior. RIM activate priming by disrupting Munc 13 homodimerization vesicle fusion, and Ca^{2+} ion channel would occur and induce synaptic plasticity. The dynamics of synaptic plasticity comes from the changes of these molecules. As a result, mice exposed to EE showed significant improvements in rotarod and ladder walking performances compared to SC mice. To summarize, we confirm that EE induces recovery of the motor function by studying animal models' behavior, and we attribute the recovery to the significant increase in presynaptic proteins such as RIM in the brain. By studying the functions of these presynaptic proteins, we hope to shed light on the understanding of damage recovery in various brain/neural disease.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

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Title: Could mirror therapy help train wrist and fingers flexors spasticity inhibition? A chronic stroke patient case study

Authors: *A. BENGOETXEA[1,2], N. IRASTORZA-LANDA[3,4,5], L. SANTISTEBAN[6], C. CHUECA[7,8], M. GARRUES-IRISARRI[6], A. SARASOLA-SANZ[10,3,4], A. GARZO[11], E. RAMOS[9], P. KHANNA[13,14], J. CARMENA[13,15], A. RAMOS-MURGUIALDAY[3,11], J. MCINTYRE[5,12];
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Sci. de l'Ostéopathie, Univ. Libre de Bruxelles, Brussels, Belgium; [8]Rehabil. Dept., [9]Neurosurg. Dept., Hosp. Universitario Donostia. Osakidetza (BIOEF), Donostia-San Sebastian, Spain; [10]Hlth. Div., [11]Neurotechnology Laboratories, Hlth. Div., [12]Med. Robotics Area,Health Div., TECNALIA, Donostia-San Sebastian, Spain; [13]UC Berkeley-UCSF Joint Grad. Program in Bioengineering, [14]Dept. of Electrical Engin. and Computer Sci., [15]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, CA

Abstract: A major obstacle to achieving recovery of motor function following stroke lies in the debilitating effects of muscle spasticity, e.g. the inability to inhibit activity in flexor muscles when attempting to perform an extension at the wrist. According to Aguiar et Baker (2018), in healthy subjects when one activates wrist extensor muscles 30ms or 70 ms prior to perform an H-reflex test on wrist flexors, one can observe a facilitation of flexor H-wave responses for the former and an inhibition for the latter. According to these studies, the facilitation depends on Ib afference from wrist extensor and on Ia afference from wrist flexors. They have also shown that corticospinal tract is involved in this facilitation and inhibition. In stroke patients, however, they have shown that the inhibition of the flexor H-reflex response due to wrist-extensor stimulation disappears and is replaced by facilitation. This observation means that when stroke patients try to activate the wrist extensor there is an augmentation of the reflex activity in wrist flexors, leading to a disruption of the inhibition needed to successfully perform an extension of the wrist. Based on these mechanisms, the cessation of wrist-flexor inhibition (i.e. spasticity) in stroke patients could have at least two origins: 1) loss of supraspinal inhibition for wrist flexors and/or 2) loss of spinal inhibition due to insufficient activation of extensors.
When applying a recently proposed system for post-stroke rehabilitation that relies on a brain-machine interface (BMI) coupled to a robot to move the paretic arm, overcoming spasticity has proven to be a major hurdle. In the last decades, however, fundamental and clinical research has shown positive effects of mirror therapy for the recovery of arm and hand function. Based on the studies described above, we hypothesized that by using movements 1) encourages central inhibition of tonic flexor activity and 2) increases motor unit recruitment of wrist extensors, we could use mirror therapy to reduce the spasticity of the limb. We therefore asked a chronic stroke patient to perform mirror therapy with 1) ballistic movements that require inhibition of tonic activity by premotor cortex and 2) movements against resistance to increase the required extensor activation and further suppress flexor activity via the inhibitory action of 1b reafference. Here we will show decreases in wrist and finger flexor activity and increases of wrist and finger extensor activity during mirror therapy that has been targeted to reduce spasticity at the wrist and fingers, as described above. This was observed following 20 months of BMI training coupled with mirror therapy and active movements.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.15/H10

Topic: C.09.Stroke

Title: BCI-controlled functional electrical stimulation and robotic glove assistance for upper limb motor rehabilitation in severely impaired chronic stroke patients within a longitudinal personalized trial: The avancer clinical trial approach

Authors: C. BIGONI[1], E. BEANATO[1], **A. ESPINOSA**[2], A. CREMA[3], M. COSCIA[2], M. J. WESSEL[1], G. SPIGONI[2], S. MICERA[1], *T. L. LAABS[2], N. BIRBAUMER[2], F. C. HUMMEL[1]; [1]Ecole Polytechnic Federale de Lausanne, Lausanne, Switzerland; [2]Wyss Ctr. for Bio and Neuroengineering, Geneva, Switzerland; [3]Univ. of Geneva Med. Sch., Geneva, Switzerland

Abstract: Upper limb motor deficits in severe stroke survivors often remain unsolved. Novel neurotechnologies may support upper limb motor recovery in this subgroup if suitably combined and administered. We propose a personalized, neurotechnology-based upper limb rehabilitation strategy using a two-to-one individual based cumulative longitudinal intervention combining different neurotechnologies. Two interventional steps are provided sequentially. In the first one, a hybrid BCI able to non-invasively detect motor intention triggers a robotic glove that assists-as-needed paretic hand movements, and supramotor threshold FES to activate 6 muscles of the affected upper limb to induce movements of different complexity. Motor intention is detected from up to 16 EEG channels and from the EMG activity of up to 8 muscles in the paretic arm. The motor rehabilitation exercises include upper limb mobilization and functional tasks. In the second step, 20 minutes of tDCs of the motor cortex is administered on top of the previous intervention. Switch from the first to the second intervention and from the second to the end of therapy is individualized on the ongoing functional improvement, continuously monitored with the wrist and hand sections of the Fugl-Meyer scale, when this reaches an individual functional plateau. Clinical and quantitative assessments are longitudinally performed, including structural and functional MRI, TMS and EEG-/EMG-based evaluations. Up to 40 severe hemiparetic chronic stroke patients will be enrolled in 2 groups. One group will start immediately the therapy upon recruitment; the other will start the therapy three months after to assess spontaneous motor recovery (control condition). The individual patient study design allows each patient to train as long as necessary to achieve a maximal treatment magnitude and functional improvement. The study design allows to compare the impact of each therapy step within and between individuals, contributing to extend the knowledge on the dynamics and mechanisms of neurorehabilitation processes. Compared to ‘one suits all’ treatment strategies, such a personalized interventional strategy offers an ideal scenario to maximize treatment effects in severe chronic patients in whom no further spontaneous remission is expected.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

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Program #/Poster #: 478.16/H11

Topic: C.09.Stroke

Support: Charles H. Smith Endowment Fund

Title: A novel gene therapy approach to treat hemorrhagic stroke in mouse striatum through direct astrocyte-to-neuron conversion technology

Authors: *F. YANG[1], Y. CHEN[2], X. HE[2], Z. LIU[2], G. CHEN[3];
[1]The Dept. of Biol., [3]Biol., [2]The Pennsylvania State Univ., University Park, PA

Abstract: Intracerebral hemorrhage (ICH) is induced by rupture of arteries in the brain as a result of hypertension, aneurysm or other blood vessel abnormalities. Low oxygen environment induced by ICH causes reactive astrogliosis, neuronal death and corresponding functional deficits. Currently, none of the treatment methods provide an effective way to rescue the loss of neurons. Our lab previously demonstrated that reactive astrocytes in the ischemic injured cortex can be directly converted into functional neurons through overexpression of a single transcriptional factor NeuroD1 (Chen et al., BioRxiv, 2018). In this work, we use collagenase to induce ICH in mouse striatum, and then use adeno-associated virus (AAV) to overexpress transcription factors in the reactive astrocytes induced by ICH. After 3 weeks, we found a substantial number of the AAV-infected astrocytes showed neuronal morphologies, and were immunopositive for neuronal marker NeuN. Many of these astrocyte-converted neurons were also immunopositive for GABA and DARPP32, which are typical markers for the medium spiny neurons in the striatum. We also found that the infarct volume caused by ICH decreased after astrocyte-to-neuron conversion according to the MRI imaging analysis. We are currently conducting behavioral tests to investigate whether our novel gene therapy approach can promote functional recovery after *in vivo* astrocyte-to-neuron conversion in the ICH mouse model. Our research suggests that direct astrocyte-to-neuron conversion technology may provide a novel therapeutic treatment for ICH through high efficiency of neuroregeneration to replenish the lost neurons.

Disclosures: **F. Yang:** None. **Y. Chen:** None. **X. He:** None. **Z. Liu:** None. **G. Chen:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.17/H12

Topic: C.09.Stroke

Support: NIH R01 NS094384
NIH R01 NS085167

Title: The intensity of vagus nerve stimulation determines efficacy in improving recovery or motor function after stroke

Authors: *T. DANAPHONGSE, D. PRUITT, M. LUTCHMAN, N. PATEL, P. REDDY, V. WANG, A. PARASHAR, M. KILGARD, S. HAYS;
The Univ. of Texas at Dallas, Richardson, TX

Abstract: Vagus nerve stimulation (VNS) paired with rehabilitative training enhances recovery of function in multiple animal models of stroke and brain injury and is currently under investigation for use chronic stroke patients. Identification of the most effective methods for delivering VNS is of crucial importance to maximizing therapeutic benefit. Previous studies suggest that VNS-dependent recovery of motor function is supported by plasticity within central networks, and the extent of invoked cortical plasticity is determined by varying parameters such as stimulation intensity. In this study, we sought to determine the optimal stimulation intensity to maximize recovery of motor function after stroke. Rats trained on the supination assessment task were given ischemic lesion in motor cortex and separated into groups receiving varying stimulation intensities (0.4 mA, 0.8 mA, and 1.6 mA) paired with post-lesion motor training. Our data indicates that 0.8 mA stimulation intensity results in maximal motor function recovery when compared to other stimulation intensities. Functional recovery also generalized to an untrained task that assessed forelimb use asymmetry. We then injected a retrograde tracer virus into the trained forelimb to investigate whether corticospinal connectivity was associated with motor function recovery. Rats receiving 0.8 mA VNS demonstrated significantly greater corticospinal connectivity than rats in other groups. The results of this study suggest stimulation intensity determines efficacy of VNS therapy when paired with motor training, and that 0.8 mA proves more effective than other intensities that were tested.

Disclosures: T. Danaphongse: None. **D. Pruitt:** None. **M. Lutchman:** None. **N. Patel:** None. **P. Reddy:** None. **V. Wang:** None. **A. Parashar:** None. **M. Kilgard:** None. **S. Hays:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.18/H13

Topic: C.09.Stroke

Support: NIH Grant NS056839

Title: Effects of remote limb ischemic conditioning in conjunction with rehabilitation training after acute and chronic motor cortical infarcts in rats

Authors: *B. R. BARKSDALE[1,3], A. K. LEE[2], J. L. ROSOW[2], M. S. NICOT-CARTSONIS[2], D. F. MIRANDA-SOHRABJI[2], T. A. JONES[1];
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Abstract: Stroke survivors are often left with chronic disability due to hemiparesis of the upper limb, even after medical and rehabilitation care. Adjunctive therapies that can enhance neuroplasticity during effective motor rehabilitation (RT) is a current focus in the field. One such promising therapy is remote limb ischemic conditioning (RLIC) which is a safe and non-invasive procedure that consists of causing shorts bouts of ischemia to a limb. RLIC has been shown to enhance the learning of motor tasks in healthy adults (Cherry-Allen et al., 2015; 2017; Sutter et al.,2018). However, recent findings suggest that RLIC does not improve motor recovery compared to RT alone in the subacute phase, at least not in middle-aged rats (Barksdale et al., 2018, SfN abstract). The aim of these studies was to determine the effect of RLIC on motor recovery when added to RT during the chronic phase in middle-aged rats and in the subacute phase in young adult rats. Male Long-Evans rats were trained on the single pellet reaching (SPR) task until proficiency was reached and then a surgery was performed to model a cortical stroke by applying endothelin-1 to the caudal forelimb area of the motor cortex. Rats were aged 8 mos in the chronic study and 4-5 mos in the subacute study. RT was started 7 days in the subacute study or 6 weeks post-op in the chronic study and consisted of SPR for 60 trials every day for 14 days. RLIC was administered every 48 hours during RT. RLIC consisted of a blood pressure cuff being applied to the hindlimb and inflated above 200 mmHg for 3 cycles of 5 minutes on and 5 minutes off under isoflurane anesthesia. A control group did not have the blood pressure cuff inflated but was kept under isoflurane for the same amount of time. Ischemia was confirmed by skin temperature drop and/or color change of the hindlimb paw. Performance on the SPR, Schallert Cylinder, and Foot Fault tasks was assessed pre-op, post-op, and post-RT. Current results suggest that RLIC does not enhance motor recovery in the chronic phase of stroke in middle-aged rats. Preliminary data will be presented on the effects in the subacute phase in young adult rats.

Disclosures: **B.R. Barksdale:** None. **A.K. Lee:** None. **J.L. Rosow:** None. **M.S. Nicot-Cartsonis:** None. **D.F. Miranda-Sohrabji:** None. **T.A. Jones:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.19/H14

Topic: C.09.Stroke

Support: NS057255
NS058710
NS062097
NS075338
AHA 0840110N

Title: Direct reprogramming of reactive astrocytes to mature neurons reduces Glia scare formation and enhances neuronal repair after ischemic stroke

Authors: *M. Q. JIANG[1], S. YU[1], L. WEI[2];
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Abstract: Regenerative therapies including cell transplantation have been extensively investigated in recent years for the treatment of CNS injuries such as stroke. In the present investigation, we explored an innovative stroke treatment of reprogramming endogenous astrocytes into induced neurons (iNeurons) for neuronal repair after focal ischemic stroke. A mCherry tagged NeuroD1 lentivirus was generated under a mouse GFAP promoter for *in vitro* and *in vivo* infections. Cultured astrocytes expressing mCherry/NeuroD1 adopted neuronal morphology and expressed neuronal markers Tuj-1, NeuN, and synaptic proteins 2-4 weeks after infection. Proliferation was drastically reduced compared to control cultures. Converted cells developed significantly longer processes (>20-100 mM) inspected at 6 weeks after infection. A focal ischemic stroke of the right sensorimotor cortex was induced in adult GFAP-Cre x Rosa-YFP mice. Astrocytes from this mouse remain YFP positive regardless of cell phenotype. The lentivirus containing mCherry-NeuroD1 and the GFAP promoter was injected into the peri-infection region 3 days after stroke, which transduced ~10% of reactive astrocytes accumulated in the peri-infarct region. Six weeks later, converted cells were identified by the co-labeling of YFP (the astrocyte origin marker), mCherry (the marker for NeuroD1 transduction), and NeuN (mature neuron marker). Around ~60% of converted cells expressed NeuN and showed neuronal morphology. Western blot assay of the peri-infarcted region detected significant higher levels of BNDF and FGF10 in NeuroD1-transfected mice compared to animals received empty vector. Meanwhile, the area of gliosis noticeably decreased. Stroke mice received NeuroD1 transfection performed significantly better in the rotarod test and corner test and showed a preventive effect

on chronically developed depressive behavior 4 months after stroke. Thus, astrocyte to neuron reprogram enforces parenchymal neurogenesis and helps to improve functional recovery after stroke.

Disclosures: M.Q. Jiang: None. **S. Yu:** None. **L. Wei:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.20/H15

Topic: C.09.Stroke

Title: A novel approach for training eye hand coordination using tracking sensors with emerging user interface in chronic stroke survivors - A randomized controlled study

Authors: *M. CHOUDHARY[1], N. CHOUDHARY[2];
[1]Shree IG Hosp. and Active Hlth. Ctr., Jodhur, India; [2]Physiotherapy and Rehabil., Government Physiotherapy Col. (dr. S.N. Med., Jodhpur, India

Abstract: Background and Aims
Eye-hand coordination is essential for humans, as many activities in daily life require precise eye and hand functions. The stroke survivors have poorer eye-hand coordination when using their hemiparetic hand. A significant correlation exists between eye-hand coordination performance and hand function test scores. The aim of this study was to develop a low cost system for testing and training eye and hand coordination using gamification as a tool for improving hand function in chronic stroke patients.
Methods
6 subjects (mean age 63.2± 4.3 years) with chronic stroke were screened and randomized into experimental and control groups with n=3 each. Both groups received 1 hour of standard upper limb physical therapy, 6 days a week for total 4 weeks. Experimental group also played a customized eye hand coordination game called "HandEye" using Tobii Eye X® and Leap Motion® for 3 sessions of 2 minutes each. Primary outcome measure was BBT (Box and Block Test).
Statistical Analysis
Statistical analysis was done using SPSS version 22. The change in outcome measure from pre to post intervention was evaluated separately in each group and compared using ANOVA. A p-value of less than 0.05 was considered as significant. The correlation between eye hand coordination testing and primary outcome measure was done in the experimental group using Pearson’s correlation coefficient.
Results
A significant improvement in scores of BBT was found in both experimental (F=234.244,

p<0.001) and control (F=85.099, p<0.001) group from pre to post intervention but the change in BBT scores were higher in experimental group. The difference between change in BBT scores from pre to post intervention were significant (F= 52.071, *p*<0.001). Pearson's correlation analysis revealed a highly positive relationship (r^2 = 0.604; p <0.01) between scores of HandEye and BBT of the hemiparetic extremity in the experimental group.

Conclusion

Natural user interface technology and gamification techniques can be useful for hand rehabilitation in stroke survivors.

Figure 1. Subject playing HandEye game.

Disclosures: **M. Choudhary:** None. **N. Choudhary:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.21/H16

Topic: C.09.Stroke

Support: Illinois Wesleyan University Artistic and Scholarly Development Grant

Title: Differences in functional recovery and kinematic reach analysis after task specific and task non-specific rehabilitation in a mouse model of stroke

Authors: R. TOMAZIN[1], A. GOURLEY[1], E. STANKUTE[1], L. EBERT[1], *A. L. KERR[2]; [2]Psychology, Neurosci., [1]Illinois Wesleyan Univ., Bloomington, IL

Abstract: Stroke results from a blockage in blood supply (ischemic) or a bleed (hemorrhagic) in one hemisphere of the brain. Worldwide, approximately 10 million people are left with moderate to severe disability due to stroke, with the most common deficit being upper extremity impairment. Current stroke rehabilitation strategies utilize task specific training of a skill, meaning one practices the specific skill they want to regain. However, it is possible that there are more transferrable types of rehabilitation that target skilled use can generalize to similar tasks and may be as effective in rehabilitating debilitated skills. The current study utilized several skilled reaching tasks (e.g., the Pasta Matrix Reaching Task and the Single Pellet Reaching Task) in a photothrombotic mouse model that show parallels to human dexterous movements in order to observe the functional effects of task specific versus task non-specific upper extremity rehabilitation post-stroke. We also used kinematic analysis of the SPRT to understand the quality and differences of skilled reach behaviors between groups after stroke and rehabilitation. All mice were pre-operatively trained on the SPRT to establish the skill. Following photothrombotic stroke, mice were separated into three groups for a total of 10 days of rehabilitative training: SPRT (task specific), PMRT (task non-specific), and control. Following 10 days of rehabilitative training, all mice were again assessed on the SPRT. Though we did not detect differences in functional outcome between animals receiving SPRT or PMRT rehabilitative training, we did observe significant differences in degree of abnormality of the skilled reach post rehabilitative training between task-specific, task non-specific, and control rehabilitative training groups. This may indicate that task specific rehabilitative strategies may promote more true recovery due to the lesser degree of abnormalities in movement post-training as compared to task non-specific therapy and control groups. Task non-specific training, while beneficial for functional outcome, may result in more compensatory movements.

Disclosures: R. Tomazin: None. **A. Gourley:** None. **E. Stankute:** None. **L. Ebert:** None. **A.L. Kerr:** None.

Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 478.22/H17

Topic: C.09.Stroke

Support: Illinois Wesleyan University Artistic and Scholarly Development Grant

Title: Intermittent rehabilitative training is protective, but not functionally beneficial, following stroke in C57BL/6 mice

Authors: *V. NEMCHEK[1], E. M. HAAN[1], V. PAVLIK[1], A. L. KERR[2];
[2]Psychology, Neurosci., [1]Illinois Wesleyan Univ., Bloomington, IL

Abstract: Stroke is a leading cause of disability worldwide. Focused training of the impaired limb has been shown to improve its functional outcome in animal models. However, most human stroke survivors exhibit persistent motor deficits. While there are many possibilities to explain these discrepancies, one likely contributing factor is the difference in rehabilitation intensity between experimental (animal) and clinical (human) settings. The current study investigated the effect of training intensity on behavioral outcome in a mouse model of stroke. After learning a skilled reaching task, mice received a unilateral photothrombotic stroke to the forelimb representation area of sensorimotor cortex, affecting the preferred reaching limb. Post-operatively, animals received either daily rehabilitative training, intermittent rehabilitative training (every other day), or no rehabilitative training. Each training group completed 14 total rehabilitation sessions; the daily group completed them in 14 days and the intermittent group competed them in 28 days. Assessment of the impaired limb after rehabilitation illustrated that daily training resulted in significantly better performance than no training. The intermittent group fell between the other two groups, being statistically significantly different than both daily training and no training conditions. Interestingly, intermittent training appeared to protect against functional decline observed in control mice, which did not train, without improving reach ability beyond the initial stroke deficit. Our results indicate that intensity of rehabilitation is important for optimal recovery, with intermittent training being enough to protect against functional decline but not enough to provide significant behavioral gains.

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Poster

478. Non-Pharmacological Approaches for Stroke Therapy and Recovery

Location: Hall A

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Topic: C.09.Stroke

Support: National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2016R1A2B4012054)
National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2018R1D1A1A02086038)

Title: Serum levels of BDNF in subacute and chronic stage after stroke

Authors: *K. KIM[1], H. KIM[2], A. LEE[2], Y.-H. KIM[2], W. CHANG[3];
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Abstract: Introduction: Brain-derived neurotrophic factor (BDNF) is involved in neuroplasticity in both the intact and the damaged brain. Although serum BDNF is used as a biomarker in major depressive disorder and bipolar disorder, there was a lack of reports with serum BDNF about neuroplasticity in stroke patients. In this study, we aimed to investigate the potential of BDNF as biomarker in neuroplasticity by serial analyzing the serum BDNF from subacute to chronic stage in stroke patients. **Methods:** Ninety-two stroke patients (mean age 63.1 yrs) were recruited in this study. We measured the serum BDNF, proBDNF and MMP-9 at T0 (2 weeks after onset), T1 (4 weeks after onset) and T2 (3 months after stroke onset) in each participant. In addition, all participants were assessed with NIH Stroke Scale (NIHSS) for stroke severity, Fugl-Meyer assessment (FMA) for motor function and for Korean Mini-Mental State Examination (K-MMSE) for cognitive function at three time points. Repeated measures ANOVA with Bonferroni correction were performed to determine the serial change from T1 to T3. **Results:** Each stroke severity, motor and cognitive function showed significantly improvement from T0 to T2 ($p<0.05$). There was no significant difference between serum BDNF at T0 and T1. Serum BDNF at T0 and T1 tended to higher than that at T2 without statistical significance. ProBDNF and MMP-9 significantly decreased serially from T0 to T2. In addition, proBDNF and MMP-9 showed significantly higher at T0 and T1 than T2, respectively ($p<0.05$). **Conclusion:** It is well known that the neuroplastic potentials decrease from subacute to chronic stage in stroke patients. Therefore, the results in this study may suggest that serum proBDNF and MMP-9 could be used as biomarker for neuroplasticity in stroke patients. However, further study should be needed to clarify these results considering functional improvement in stroke patients. Support National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2016R1A2B4012054) National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIP) (NRF-2018R1D1A1A02086038)

Disclosures: K. Kim: None. **H. Kim:** None. **A. Lee:** None. **Y. Kim:** None. **W. Chang:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.01/H19

Topic: C.10. Brain Injury and Trauma

Support: COBRE II GM103642
PRCTRC Pilot Project

RCMI U54MD007600
UPR MSC Chancellor's Office
UPR MSC School of Medicine Deanship
Brain and Behavior Research Foundation (NARSAD)

Title: Effects of closed head injury on short term memory in rats

Authors: *O. MARTÍNEZ GUZMAN[1], M. CACERES-CHACON[1], M. RIVERA-LÓPEZ[1], R. Y. RAMOS-SÁNCHEZ[2], D. M. OJEDA[2], D. SIERRA-MERCADO[1];
[1]Anat. and Neurobio., Univ. of Puerto Rico Sch. of Med., San Juan, PR; [2]Univ. of Puerto Rico Rio Piedras Campus, San Juan, PR

Abstract: Approximately 4 million cases of traumatic brain injury occur yearly in the United States. The most common form of brain injury, concussion, is frequently seen in sports and combat. The brain movement within the skull caused by concussion leads to diffuse axonal injury through tearing of neuronal axons, which may lead to motor and cognitive dysfunction. However, the susceptibility of specific behaviors such as short-term recognition memory to concussion remains unclear. We hypothesize that concussion will impair short-term memory. Concussion can be modeled in rodents with a closed head injury (CHI). Here, a guide tube was placed above the head of anesthetized male rats, and a 260g weight was dropped from a height of 42cm, impacting the animal's head. At impact, free rotation of the head downward occurred due to displacement of the underlying surface. To assess the effects of CHI on memory, a novel object recognition test (NOR) was performed (Sham: n=4, CHI: n=4,). In the NOR, a rat is placed in an open field with a familiar and novel objects and time spent with each object is recorded. CHI caused a decreased ratio of time spent with the novel object (Sham: 0.41, CHI: 0.65; p=0.0461) indicating a deficit in a short-term recognition memory. To test for motor deficits, distance traveled, and speed were recorded in an open field. Notably, no motor deficits were detected. Thus, cognitive deficits may occur independent of effects on motor function. Next, we will assess activity in brain regions involved in recognition memory.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.02/H20

Topic: C.10. Brain Injury and Trauma

Title: Release of adenosine triphosphate into the extracellular space in a rat model of mild traumatic brain injury

Authors: *K. KAMIYA[1], H. NEGISHI[1], Y. TAKAMINE[1], Y. FURUKAWA[2], M. KOBAYASHI[2], T. KUMAGAWA[3], K. SHIJO[1], N. MORO[2], T. MAEDA[4], A. YOSHINO[1];
[2]Neurosurg., [3]Neurolog. Surgery, [4]Neurolog. Surgery & Anesthesiol., [1]Nihon Univ. Sch. of Med., Tokyo, Japan

Abstract: Glutamate is known to be released into the extracellular space immediately after concussion in a rat fluid percussion model. Another important transmitter in the brain is adenosine triphosphate, although the trend of adenosine triphosphate after concussion is not known. We used a close head injury model to create concussion and measured the value of glutamate and adenosine triphosphate by a biosensor before and after injury. Glutamate value increased immediately following injury as reported previously. The adenosine triphosphate value in the extracellular space raised immediately after insertion of biosensor in a non-injured rat cortex due to stab wound injury. But the adenosine triphosphate value of the injured rat showed higher value compare to non-injured rat. Western blot analysis did not show increase of activated microglia at least after single concussion injury.Both glutamate and adenosine triphosphate are released immediately after concussion injury in rat.

Disclosures: K. Kamiya: None. **H. Negishi:** None. **Y. Takamine:** None. **Y. Furukawa:** None. **M. Kobayashi:** None. **T. Kumagawa:** None. **K. Shijo:** None. **N. Moro:** None. **T. Maeda:** None. **A. Yoshino:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.03/H21

Topic: C.10. Brain Injury and Trauma

Support: NIH/NINDS TOP-NT: 1UG3NS106945-01
NIH/NINDS SBIR: R43NS106972-01
BRAINBox Solutions SRA20174377

Title: Astrocyte injury defined biomarker associate with neuro-vascular unit compromise acutely after rat controlled cortical impact

Authors: *I. B. WANNER[1], H. ABDIRAHMAN[1], I. BONACORSI[1], V. PARRILLI[1], M. WALKER[2], N. HARRIS[2];
[1]Semel Inst., [2]Dept. of Neurosurg., UCLA, Los Angeles, CA

Abstract: Key for translating preclinical neurotrauma studies into clinic are the use of same noninvasive biomarkers. Traumatic brain injury (TBI) compromises neurovascular unit integrity with risk to neurological function. The pericontused cortex is an urgent clinical priority as tissue

surrounding the impact site has potential for recovery. This project established reproducible cytometric and noninvasive biomarkers acutely after controlled cortical impact (CCI) in adult male and female rats. Novel astrocyte injury defined (AID) biomarkers were used to define acute TBI phenotypes and to link biofluid and cellular injury metrics. AID biomarkers were aldolase C (ALDOC), glial fibrillary acidic protein breakdown products (GFAP-BDPs), glutamine synthetase (GS) and astrocytic phosphoprotein 15 (PEA15, Halford et al., 2017). Rat immunoglobulin (IgG) levels marked blood-brain barrier breach and blood extravasation on coronal vibratome sections. Glial and vascular injuries were compared to neuronal damage measured by pan-neurofilament (NF) and NeuN. Images were systematically analyzed using thresholding and structural feature segregation in Fiji. Cerebrospinal fluid (CSF) was drawn via cisterna magna puncture. Serum from tail vein blood was depleted using albumin-binding magnetic beads. Biofluids and recombinant protein calibrants were measured by immunoblotting with rat IgG-preadsorbed antibodies. Pericontused gray matter was defined by engorged veins, via MRI and histology, by interstitial bleeding and by NeuN reduction. Pericontused neuropil had reduced NF levels and a unique profile of fiber fragmentation. Automated skeleton analyses of GS signals documented fewer processes in pericontused versus sham astrocytes. Intact gray matter astrocytes had high levels of somatic ALDOC whereas pericontused swollen astrocytes were ALDOC depleted. Disperse interstitial and capillary ALDOC signals were measured and validated by recombinant ALDOC competition. ALDOC, GS and PEA15 levels were elevated in CSF and serum acutely (30 min - 5 hrs) and 24 hrs after CCI versus sham. GFAP-BDPs were elevated at 24 hrs postinjury in CSF and serum. Hemorrhagic injury cores had damaged astrocytes displaying a pathological GFAP pattern. In conclusion, AID markers defined astroglial injury types that coexist with neuronal and vascular injuries. They manifest acutely compromised neuro-vascular units in the pericontused cortex that were distinct from the impact core. Thus, AID biomarkers act as noninvasive surrogates of these injury types. Biomarkers of brain tissue compromise and loss can facilitate diagnosis, classification and treatment monitoring of TBI patients.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.04/H22

Topic: C.10. Brain Injury and Trauma

Support: Phoenix Children's Hospital Mission Support

Title: Juvenile rat cognitive performance is preserved after diffuse traumatic brain injury with self-guided rehabilitation

Authors: *J. B. ORTIZ[1], L. LAW[2], D. R. GRIFFITHS[3], U. S. AFTAB[4], P. D. ADELSON[5], J. LIFSHITZ[6], R. K. ROWE[7];
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Abstract: A traumatic brain injury (TBI) experienced early in life affects developmental and functional outcomes, especially when left untreated. Clinical and experimental TBI disrupt cognitive performance, for which a critical need arises to develop rehabilitation strategies that mitigate cognitive and motor deficits. We hypothesized that rehabilitation targeting spatial and contextual memory circuits would prevent the onset of injury-induced cognitive impairments in juvenile rats. Rehabilitation occurred in a box with a peg board floor (24”x24”) that allowed 3” plastic pegs to be inserted at 1” intervals in designated layouts (Peg Forest Rehabilitation; PFR). Male and female juvenile rats (post-natal day 35; n=24) were subjected to sham or midline fluid percussion injury. Beginning one week post-injury, rats were exposed to either PFR or cage control exploration (15 min/day). PFR allowed free navigation through random configurations of the peg-filled arena for 10 days over 2 weeks. Control rats remained in their home cage in the center of the arena with the peg-board removed for 15min/day/10days. One week post-rehabilitation (1 month post-injury), cognitive performance was assessed for short-term (novel object recognition; NOR), long-term (novel location recognition; NLR), and working (temporal order recognition; TOR) memory performance calculated as a discrimination index between novel and familiar objects. An overall effect on NOR discrimination index existed in females ($F(3,8)=4.050$, $p=0.050$), with TBI-PFR rats having the highest discrimination index. Overall effects existed on percent time spent between objects in NOR (males: $F(3,8)=59.67$, $p<0.001$; females: $F(3,8)=14.67$, $p=0.0013$), NLR (females: $F(3,8)=5.667$, $p=0.0222$), and TOR (males: $F(3,8)=12.67$, $p=0.0021$) tasks. Thus, the self-guided, intermittent PFR that involves dynamic, novel spatial navigation can prevent TBI-induced cognitive impairment in juvenile rats. PFR serves as a therapeutic intervention to investigate cellular and molecular mechanisms of effective rehabilitation. Spatial navigation training may have clinical relevance.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.05/H23

Topic: C.10. Brain Injury and Trauma

Support: VHA RR&D Award #IK2 RX002488

Title: Effects of chronic repetitive mild traumatic brain injury on intra-op and post-op weight gain in adult male Sprague Dawley rats

Authors: *M. A. GRAHAM[1,2], P. T. JUZANG[1,2], T. E. WHITE[1,2];
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Abstract: Traumatic brain injury (TBI) is a major health concern, with mild TBI (mTBI) being the most common type of injury. This is especially true for the military population, in that there were 4300 reported cases of TBI among active-duty military service members in 2018, where more than 84% were classified as mTBI. Anthropometric measures such as weight gain/loss are key standards of health and wellness assessment, and are often used to indicate recovery milestones following injury. While they have been reported, there is a remarkable lack in the evaluation and implications of these measures in TBI research, particularly in preclinical models. In this study, we aimed to determine if a model of chronic repetitive mTBI (rmTBI) affects weight gain adult male rats. Twenty-four adult male Sprague Dawley rats (226-250 g at time of arrival) were randomly assigned to one of two groups: SHAM (n=12) and TBI (n=12). A craniotomy was performed on all animals with a trephan drill bit (6 mm diameter) with the center 4 mm posterior and 3-4 mm lateral to bregma. Chronic rmTBI was performed on TBI animals using a unilateral mild controlled cortical impact injury administered in 5-day intervals over the course of 15 days (4 injuries total - one every 5 days). Three weeks of behavioral testing was conducted 14 weeks post-injury. Animals were weighed immediately prior to each surgical procedure during the intra-op period (four measurements total), once weekly for 17 weeks during the post-op period, and on the day of sacrifice. Three data points were recorded for each weight measurement: overall weight, weight gained per time point, and total weight gained. TBI animals weighed a mean 18.75 ± 11.62 g less overall ($p=0.036$) g at intra-op day 15, gained a mean 6.25 ± 2.89 g less weight between intra-op days 10 and 15 ($p=0.041$), and gained a mean 11.98 ± 7.93 g less total weight through intra-op day 15 ($p=0.043$) than SHAM animals. No significant differences were detected prior to intra-op day 15 or at any time point during the post-op period, though some notable trends were observed. Chronic rmTBI seems to have a gradually increasing negative effect on weight gain in male rats during the intra-op period. This effect may be attributed to the stress and pain of the surgical procedures and repeated injuries. The lack of

differences observed during the post-op period likely resulted from the level of variability within each group, which may have been caused by differing injury recovery patterns between groups and stress from behavioral testing. The results of this study suggest that anthropometric measures, including weight gain, should be monitored closely immediately following TBI to facilitate healthy recovery from injury.

Disclosures: M.A. Graham: None. **P.T. Juzang:** None. **T.E. White:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.06/H24

Topic: C.10. Brain Injury and Trauma

Support: Support from Max Planck Society to JS
NIH grant ROINS059879 to CW
NIH grant S10RR13880 to AMW
NIH grant MH047340 to JFD
HU00001-14-1-0023 to JLD

Title: Conditioned contextual freezing is a biomarker of axonal injury in a mouse model of blast-induced mild traumatic brain injury and can be used for drug characterization

Authors: C. WEISS[1], F. R. LENDACKI[2], J. C. PINA-CRESPO[3], P. H. RIGBY[4], G. GARCIA[3], J. L. DUCKWORTH[5], J. F. DISTERHOFT[1], A. M. WYRWICZ[2], ***J. SPIESS**[6,3];
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Abstract: Problem Statement: Mild Traumatic Brain Injury (TBI) is a closed head injury caused by explosions, traffic accidents, falls and impact sports. Approximately, 80% of hospital-reported TBIs are classified as mild. An important manifestation is axonal injury identified with Diffusion Tensor Imaging (DTI) by reduced fractional anisotropy. Mild TBI is a risk factor for several degenerative and traumatic diseases including Post-Traumatic Epilepsy (PTE). Mild TBI has been related to Chronic Traumatic Encephalopathy (CTE) generated by hyperphosphorylated tau protein proposed as mild TBI biomarker. However, this correlation does not seem to hold in all traumatic situations related to mild TBI.
Objective: In a first experiment, we investigated if conditioned fear generated by delay or trace fear conditioning could serve as a biomarker for mild TBI identified by reduced fractional anisotropy. In a second experiment, we applied this biomarker concept to the sodium channel

blocker 5,5-diphenylhydantoin (phenytoin), an antiepileptic drug.
Methods: In the first experiment, male C57BL/6N mice, single-housed, anesthetized with isoflurane, body-protected with nylon coats and foam ear plugs, were exposed to a 1.4 msec supersonic helium wave from a 6 feet long and 2 inches wide aluminum tube on Day 1. The reflective pressure was 56.9 psi at the mouse head. On Day 3, all mice were subjected to training for auditory trace or delay fear conditioning, models of declarative and non-declarative memory, respectively. On Day 4, all mice were tested for conditioned fear, and on Day 5, the animals were cardioperfused, and their brains were analyzed in a 14.1 TESLA MR imager. In the second experiment, blast and fear conditioning were run as before except for phenytoin being i.p. injected (10 mg/kg) into the anesthetized animal during preparation for the blast.
All three major behavioral expression modes of fear conditioning: contextual freezing (to the training context), preCue and Cue freezing were analyzed.
Results: The main significant inverse correlation was found between contextual freezing and fractional anisotropy in the lateral corpus callosum (r=-0.603, Z=-3.56, p=0.0004) and to a slightly lesser extent in the medial corpus callosum (r=-0.464, Z=-2.562, p=0.0104). Thus, conditioned contextual freezing was qualified as biomarker of blast-induced mild TBI. Phenytoin enhanced contextual freezing and thus axonal injury after blast with all pathological consequences related to mild TBI to be considered. It is important to realize that this action requires a preceding traumatic event. This may be a mechanism to explain observed clinical problems of phenytoin application in PTE.

Disclosures: C. Weiss: None. **F.R. Lendacki:** None. **J.C. Pina-Crespo:** None. **P.H. Rigby:** None. **G. Garcia:** None. **J.L. Duckworth:** None. **J.F. Disterhoft:** None. **A.M. Wyrwicz:** None. **J. Spiess:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.07/H25

Topic: C.10. Brain Injury and Trauma

Title: Pramipexole counteracts the outcomes of traumatic brain injury in wistar rat on oxidative stress and behavioral dysfunction

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Abstract: Tissue damage and organelle dysfunction is the key event in traumatic brain injury (TBI) pathophysiology which leads to oxidative stress, neuronal dysfunction and cell death. There is no therapeutic medicine is available that could potentially hamper the neuronal death and dysfunction after TBI. Pramipexole (PPX) is a promising neuroprotective D2-agonist that

can work against various neurological disorders. The present study was aimed to elucidate to explore the mechanism of neuroprotection by PPX against oxidative stress induced neuronal damage and dysfunction after TBI. We hypothesized that neuroprotection by PPX may involve in amelioration of oxidative stress and mitochondrial dysfunction followed by TBI. PPX was injected intraperitoneally (0.25 & 0.5 mg/kg/b.wt.) after trauma. The behavioural assessment parameters were assessed for PPX neuroprotection at 48h and 7days post-TBI. The oxidative stress parameters glutathione (GSH), lipid peroxidation (LPO), superoxide dismutase (SOD) and catalase were analyzed spectrophotometrically at 48h after TBI. We used flow cytometry to analyze mitochondrial membrane potential (ΔΨm) which is a contributing factor of mitochondrial dysfunction after TBI. The expression level of apoptosis-inducing proteins was done by western blot analysis. Post-treatment of PPX improved neurobehavioral function and attenuates oxidative damage and ΔΨm collapse. We concluded that the neuroprotective effect of PPX is mediated by attenuating oxidative stress (LPO, SOD, GSH and catalase) and ΔΨm after TBI in experimental animals. This data provide evidence of PPX provides neuroprotection as a therapeutic approach for the treatment of TBI. **Keywords:** traumatic brain injury, control cortical impact, behavioural alteration, oxidative stress, recovery

Disclosures: **M. Salman:** None. **S. Parvez:** None. **H. Tabassum:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.08/H26

Topic: C.10. Brain Injury and Trauma

Support: R01NS094440
R21NS099605

Title: Effects of assessment timing and rat strain on auditory processing and spatial learning after mild traumatic brain injury

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Abstract: Traumatic brain injury exacts significant neurobehavioral cost on nearly 1.7 million patients and their families in the United States each year. In patients with mild traumatic brain injury (mTBI), auditory impairments and deficits in learning and memory are common, often presenting at variable time windows post injury. Rodent models employing controlled cortical impact (CCI) techniques have been used to study cellular processes and behavioral outcomes linked to injury progression. Previous studies have also reported differences in learning across rat

strains with mTBI. In the current series of studies, mTBI was induced in male Long Evans (LE; n=48) and Sprague Dawley (SD; n=24) rats using the CCI method, along with sham procedures. Subjects were subsequently assessed for auditory processing and spatial learning abilities at multiple time-points post injury in order to identify windows for deficit emergence. Results showed LE mTBI rats (n=12) with intact pure tone detection. However, significant impairments in frequency modulated (FM) sweep detection were observed as compared to sham (n=12) subjects 32 days post (DP) mTBI. A second study utilizing LE rats revealed comparable performance between sham (n=12) and mTBI (n=12) subjects in pure tone discrimination and FM sweep detection when assessed 59 DP mTBI. In study two, LE subjects with mTBI showed no deficits in spatial learning as compared to sham subjects. In study three, SD rats showed no impairments in auditory processing across single tone or FM Sweep tasks when evaluated 43 DP mTBI. However, in contrast to both LE studies, SD rats with mTBI showed significant impairments in spatial learning as compared to shams. Our findings parallel strain differences in spatial learning observed across other models of TBI. Further, it appears that deficits in FM sweep detection, seen for LE subjects tested 32DP mTBI, may be mediated by the post TBI window of assessment and strain specific variations in sensory acuity. Specifically, auditory deficits appear to be most prominent within 32 days of mTBI in LE subjects but not at later days for LE or SD subjects. Our findings may help inform the selection of optimal assessment windows and appropriate strains when employing a CCI model of mTBI.

Disclosures: S.W. Threlkeld: None. **E. Morales Cestero:** None. **D. Laflamme:** None. **A.B. Bradford:** None. **J. Szmydynger-Chodobski:** None. **A. Chodobski:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.09/H27

Topic: C.10. Brain Injury and Trauma

Support: KAKENHI #19K14491 to MN
KAKENHI #18H03507 to SY

Title: Focal brain lesion induced by ultraviolet irradiation in a rhesus monkey

Authors: *M. NAKATA, A. TAKEMURA, K. MATSUDA, S. YAMAMOTO;
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Abstract: Creating focal brain lesions is an essential technique to investigate the function of a specific brain area. Because of the anatomical resemblance to the human brain and the ability to perform advanced cognitive tasks, non-human primates (NHPs) subjected to lesion experiments have played an important role in investigations of higher brain function. However, techniques

that enable removing all of the brain tissue at a targeted site (e.g. aspiration) in NHPs cannot be easily controlled. Pharmacological techniques inactivate only specific cell types. Thus, we previously developed a novel method for creating focal brain lesions using ultraviolet (UV) light in rodents (Nakata et al., 2018, *Sci Rep*). In this study, we applied the UV lesion method to a macaque monkey. An adult male rhesus monkey (*Macaca mulatta*) was anesthetized. UV irradiation was provided through an optical fiber connected to a UV LED light source (UV-A; wavelength 365 nm, 4.0 mW × 3.0 h = 12.0 mWh). After removal of the skull, the tip of an optic cannula (flat circle, 600 μm in diameter) was stereotaxically placed on the targeted brain site (parietal cortex) and contacted the dura mater. Four days after irradiation, we performed magnetic resonance imaging (MRI), and found that the UV lesion had higher signal intensity in a T2-weighted MRI. Thereafter, the animal was perfused for histological analysis the following day. Hematoxylin-eosin staining further revealed that the UV irradiation had induced an inverted-bell shaped lesion. Loss of brain tissue and hemorrhagia were also observed in the central part of the lesioned area. Neuronal marker-immunoreactive cells were absent, and Iba1-immunoreactive microglia/macrophages were congregated within the lesion. These observations indicate that UV irradiation to the monkey brain induced neural degeneration and an immunological response. Taken together, these results show that we succeeded in applying the UV lesion method to the primate cortical surface, which was performed with simple surgical procedures and without any expert skill.

Disclosures: M. Nakata: None. **A. Takemura:** None. **K. Matsuda:** None. **S. Yamamoto:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.10/H28

Topic: C.10. Brain Injury and Trauma

Support: NIH UH3 NS095554
NIH NINDS NS067249

Title: Selective activation of central thalamic pathways facilitates behavioral performance in healthy non-human primates

Authors: *A. JANSON[1,2], J. L. BAKER[4], N. D. SCHIFF[5], C. R. BUTSON[1,2,3];
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Abstract: The central thalamus (CT) is an important component of the arousal regulation system in the brain and damage to this structure, as a result of severe brain injury, is linked to chronic cognitive impairment. Deep brain stimulation within the central thalamus (CT-DBS) has been proposed as a therapeutic strategy to improve arousal regulation and cognitive impairments in patients with severe brain injury. Our hypothesis is that fiber pathways in the central thalamus have a specific orientation, projecting to the cortex and striatum, which are robustly activated with stimulation configurations that facilitate behavioral performance and enhance cortical and striatal activity. We developed a biophysical computational model of the macaque central thalamus that includes these fiber pathway projections and correlated their activation with behavioral and physiological data collected from a single subject performing a vigilance task during CT-DBS. We found that the stimulation configurations that produced significant improvements in performance were also the configurations that activate fibers in the biophysical model based upon the subjects reconstructed lead locations, see Figure 1. Our findings provide evidence that activation of specific structural white matter pathway in the central thalamus is linked to improved performance and activation of striatal and cortical areas. We anticipate that the model-based predictions of fiber pathway activation in the macaque central thalamus will provide a direct translational target in human studies of DBS for the treatment of severe brain injury.

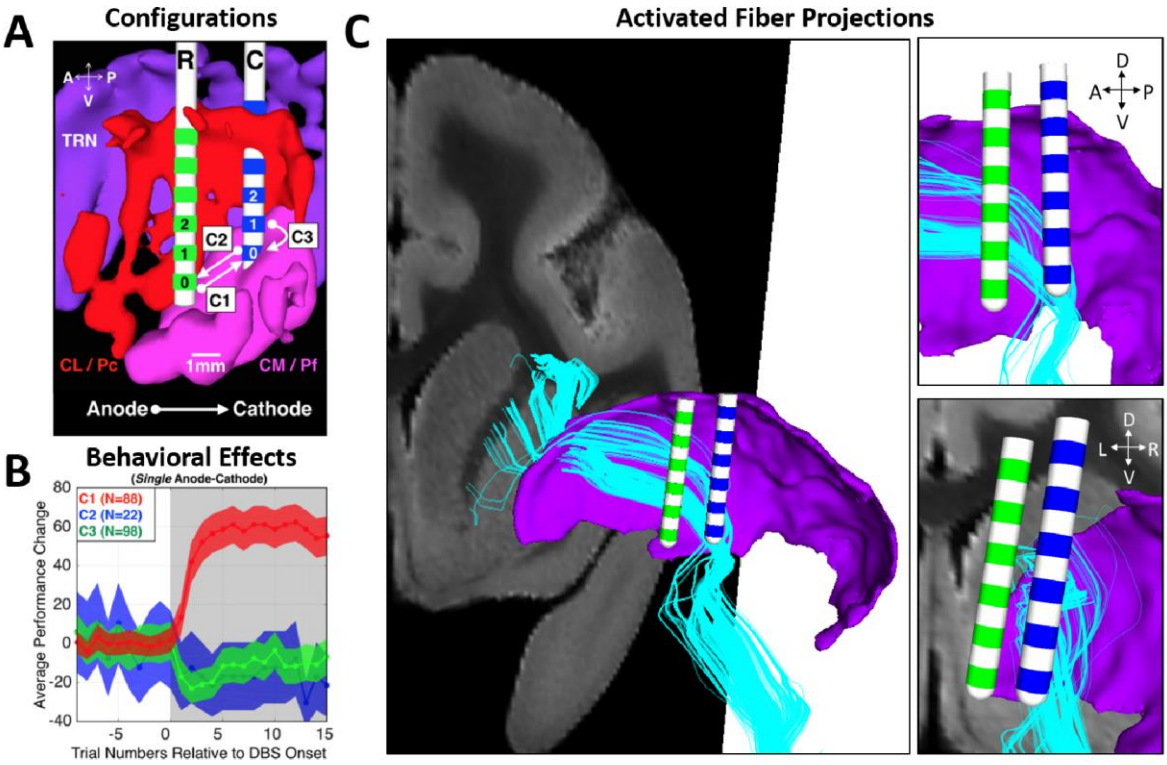

Figure 1. Configuration dependent effects of stimulation on behavioral performance and biophysical model of target fiber pathway. (A) Sagittal view of DBS lead placement in NHP subject and three different experimental stimulation configurations. Central lateral nucleus (CL) in red, central median nucleus (CM) in pink, and thalamic reticular nucleus (TRN) in purple. (B) Average performance change during stimulation for the three configurations +/- 95% CI. (C) Reconstructed fiber projections, from diffusion weighted imaging, through the central thalamus that are activated with configurations that strongly increase performance during stimulation.

Disclosures: **A. Janson:** None. **J.L. Baker:** None. **C.R. Butson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IntelectMedical. F. Consulting Fees (e.g., advisory boards); NeuroPace, Advanced Bionics, Boston Scientific, IntelectMedical, Abbott, Functional Neuromodulation.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.11/H29

Topic: C.10. Brain Injury and Trauma

Support: DoD TATRC W81XWH-13-1-0263
Concussion Legacy Foundation
Anonymous Foundation

Title: Boston University concussion scale (BUCS)

Authors: *S. CHANCELLOR[1], T. BELLIO[2], E. S. FRANZ[3], J. PIETRO[1], J. A. MONCASTER[1], O. MINAEVA[1], L. E. GOLDSTEIN[1];
[1]Sch. of Med., [2]Biomed. Sci., [3]Col. of Engin., Boston Univ., Boston, MA

Abstract: Concussion in humans is characterized by rapid onset and spontaneous resolution of a constellation of somatic, neuromotor, cognitive, and behavioral signs and symptoms precipitated by head injury with or without loss of consciousness. Neurological signs of acute concussion include confusion, altered mentation, slowed reaction time, motor weakness, impaired balance, incoordination, dystaxia, affect lability, and amnesia. Preclinical models of acute concussion have eluded development due to experimental requirements for anesthesia during injury. Recently, we showed that unanesthetized mice subjected to closed-head impact injury induced with a novel momentum transfer device reliably triggered abrupt onset and rapid recovery of a concussion syndrome similar to that in humans (Tagge CA *et al., Brain,* 2018). We developed the Boston University Concussion Scale (BUCS-1.0) as a multidimensional test battery for rapid, objective assessment of acute concussion in awake, unanesthetized mice. BUCS-1.0 comprises three 30-sec subtests (open-field, inverted wire mesh, beam walk) scored on standardized metrics (0-5) that capture graded task-specific deficits and summed as a composite score (BUCS range, 15-0). We conducted BUCS testing 2 min pre-injury (baseline), 2 min post-injury (post-injury), after 3-hr rest period (recovery). Most mice (166/203, 81.8%) exhibited mild neurological impairment (BUCS ≥10) after single impact. Fewer (32/203, 15.8%) showed moderate impairment (BUCS, 9-5). Severe impairment (BUCS ≤4) was rare (5/203, 2.5%). All mice recovered to baseline, typically in minutes and always by 3-hrs post-injury. In a revised format

(BUCS-2.0), we incorporated and validated a cognitive measure of spatial memory during the open-field subtest, which reveals that approximately 50% of impacted mice perform abnormally at 3 hours post injury compared to shams and the other subset of impacted mice. Surprisingly, we did not observe acute concussion (lowering of BUCS scores or abnormal spatial memory performance) in mice exposed to experimental blast.

Disclosures: S. Chancellor: None. **T. Bellio:** None. **E.S. Franz:** None. **J. Pietro:** None. **J.A. Moncaster:** None. **O. Minaeva:** None. **L.E. Goldstein:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.12/H30

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant UL1TR001412

Title: Variable changes in global brain connectivity resulting from traumatic brain injury

Authors: *J. NAKUCI[1], M. MCGUIRE[2], F. SCHWESER[3], D. POULSEN[3], S. E. MULDOON[4]; [1]Neurosci., Univ. At Buffalo, Buffalo, NY; [2]Dept. of Neurosurg., [3]Dept. of Neurol., Univ. at Buffalo, Buffalo, NY; [4]Dept. of Mathematics and CDSE Program, Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: White matter tracts are important for efficient communication between distant brain regions and damage to these tracts can have significant impact on brain function. Traumatic brain Injury (TBI) can cause axonal injury beyond the site of the trauma, with white matter tracts exhibiting high vulnerability. Here we use network analysis to study changes in white matter reorganization in the lateral fluid percussion injury (FPI) model of TBI in rats. Structural brain networks were constructed from diffusion MRI and we observed heterogeneity in the connectivity of both healthy and injured animals. However, in injured rats, we find: (1) a subnetwork of connections, distributed throughout the brain, with increased connectivity strengths when compared to control networks; (2) a shift in the network backbone toward the inclusion of links with shorter distances between regions when compared to controls and; (3) a subset of regions in which the prevalence of network motifs was altered. These individual differences in structural connectivity across injured rats reflect different profiles of pathology induced changes. Finally, using an unsupervised clustering analysis, we identify two subpopulations within the TBI group that align with differences in the severity of the injury, as assessed using behavioral severity scores. These results suggest that measures of global brain network structure can be used to quantify changes in brain connectivity due to injury and to further differentiate subpopulations within an injured cohort.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.13/H31

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant NS033310
NIH Grant NS065877

Title: Electrographic, behavioral and peripheral blood biomarkers of post-traumatic epileptogenesis

Authors: *U. DEVARAJ[1], A. BRAGIN[1,2], J. ENGEL, Jr.[1,2,3];
[1]Neurol., Univ. of California, Los Angeles, CA; [2]Brain Res. Inst., Los Angeles, CA; [3]Neurobio. and Psychiatry and Biobehavioral Sci., Los Angeles, CA

Abstract: Objective: To identify electrographic, peripheral blood and behavioral biomarkers for prediction of post-traumatic epileptogenesis.
Method: Fluid percussion injury (FPI) was performed on 2 month old male Sprague-Dawley rats (n=9). 50um tungsten electrodes were implanted bilaterally into the rat (1) prefrontal cortex, (2) striatum, (3) anterior and posterior perilesional area and (4) hippocampus. Wideband electrical activity was recorded immediately after TBI and for the next 2-6 months. Anxiety level and memory were tested once a week. Blood samples (1ml) were drawn during the 1st and the 2nd week after TBI. After analysis of EEG data, animals were separated in to those, that developed spontaneous seizures (E+ group) and those that did not (E- group). Rate of high-frequency oscillations (HFOs), level of anxiety and memory were compared between E+ and E- groups. Concurrently, blood serum was analyzed for, 4-hydroxynonenal (HNE-4), Matrix Metalloproteinase 9 (MMP-9) and Aquaporin 4 (AQP-4) levels, before and after TBI.
Results: Thirty percent of rats became epileptic (E+) 70% did not (E-). The rate of HFOs increased in the prefrontal cortex and hippocampus areas in the E+ group within the first two weeks, but not in the E- group. 100% in the E+ and 80% in the E- showed a decline in memory;

2, 12 and 24 weeks after TBI. We found 100% of rats in the E+ group performed poorly in the anxiety-related behavior test; 2, 12 and 24 weeks after TBI. Only 50% of the E- group showed an increase in anxiety in week 2. Blood serum analysis showed upregulation of MMP-9 in 100% of rats in both the E+ and E- groups within the 1st and 2nd week after TBI. AQP-4 decreased in 70% of E+ rats and 100% in E- rats. Blood HNE-4 increased in all the rats in the E+ group within week 1 and in just 30% in E-. No changes were found in the 2nd week in either group. **Conclusion:** The increased rate of HFOs is, so far, the only stable biomarker of epileptogenesis after TBI. Further experiments are needed to confirm or reject preliminary data suggesting that anxiety level or changes of HNE-4 in the peripheral blood could also be biomarkers of post-traumatic epileptogenesis.

Disclosures: U. Devaraj: None. **A. Bragin:** None. **J. Engel:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.14/H32

Topic: C.10. Brain Injury and Trauma

Support: NIH NINDS R01NS094396
NIH NINDS R21NS108098

Title: *In vivo* spatiotemporal patterns of oligodendrocyte and myelin damage at the neural electrode interface

Authors: *K. CHEN[1,6], S. WELLMAN[1,6], F. CAMBI[2,7], J. R. ELES[1,6], T. D. KOZAI[1,6,3,4,5]; [1]Dept. of Bioengineering, [2]Dept. of Neurol., [3]Ctr. for Neurosci., [4]McGowan Inst. of Regenerative Med., [5]NeuroTech Ctr., Univ. of Pittsburgh, Pittsburgh, PA; [6]Ctr. for the Neural Basis of Cognition, Univ. of Pittsburgh and Carnegie Mellon Univ., Pittsburgh, PA; [7]Veterans Admin. Pittsburgh, Pittsburgh, PA

Abstract: Brain implantable electrodes are emerging as a powerful tool for understanding the patterns of brain circuitry and for therapeutic applications to neurological disorders, given their ability to record extracellular action potentials *in vivo* and/or deliver electrical signals into the local region. However, the longevity and performances of implanted electrodes have shown to be adversely affected by overwhelming biological responses, including severe neuronal loss and thick glial encapsulation. While glial responses, microglia activation and astrocytes reactivity have been thoroughly examined, oligodendrocytes and their extended structure, myelin, have not been extensively investigated in the neural interfacing field, especially their roles in acute inflammatory and chronic foreign body responses. It is well-established that oligodendrocyte make myelin wrapped around axons to provide electrical insulation. In addition,

oligodendrocytes provide metabolic support to neurons through cytoplasmic myelin channels and monocarboxylate transporters. Implantation of electrodes break the integrity of oligodendrocytes, exposing these vulnerable neuroglia to mechanical distortion, oxidative stress, pro-inflammatory cytokines, and chemokines. To gain insight into the impairment of oligodendrocyte and myelin structures at interfaces, we have characterized the spatiotemporal dynamics of oligodendrocyte and myelin damage at the tissue-electrode interface using multi-photon imaging microscopy. We showed that insertion of electrodes damage myelin structures leading to the formation of protruding structures called myelinosomes. This early myelin morphological injury was observed at the interface region and the spatiotemporal dynamics of myelinosome formation was traced over time. Preliminary analysis was performed to measure the effect of implantation-induced mechanical strain on myelin alignment at the electrode interface. A morphological opening operation with line structuring elements in 11 angles is programmed in MATLAB. Each pixel whose intensity higher than filter threshold is measured. Myelin angle is calculated between line structuring element and highest opening operation direction. The weighted averages in myelin angle were 89.4766 ± 58.6676 degree at the interface, 85.9003 ± 43.3848 degree in the distal region (300 μm away from implant), and 72.7215 ± 53.2499 degree on the contralateral side. Interestingly, preliminary results indicate that myelinosome formation does not always result in degradation of the attached myelin sheath, showing that myelin has the ability to repair early damage at the electrode interface.

Disclosures: K. Chen: None. **S. Wellman:** None. **F. Cambi:** None. **J.R. Eles:** None. **T.D. Kozai:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.15/H33

Topic: C.10. Brain Injury and Trauma

Support: Minnesota Spinal Cord Injury and Traumatic Brain Injury Research Grant Program

Title: Effects of mild traumatic brain injury on widespread cortical function

Authors: *R. E. CARTER[1], E. SCOTT[1], L. S. POPA[1], J. ARONSON[1], J. DOMINQUEZ[2], L. GHANBARI[2], S. B. KODANDARAMAIAH[2], S. CRAMER[1], T. J. EBNER[1];
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Abstract: Mild traumatic brain injury (mTBI) can have serious short- and long-term consequences including executive function and cognitive abnormalities. Also, focal injury may have widespread effects beyond the site of impact, suggesting a global disruption of cortical

networks. Here we deploy a novel optically clear, morphological conformant 3D-printed polymer skull to perform mesoscopic Ca^{2+} imaging to evaluate how mTBI alters patterns of interactions across the dorsal cerebral cortex. Transgenic mice (Thy1-GCaMP6f) were subjected to a modified controlled cortical impact model (0.4 m/s, 1 mm impact depth, 85 ms dwell time) using a 3 mm 3D-printed impact tip directly to the motor cortex, to simulate mTBI, and were then immediately implanted with the polymer skull to allow for chronic imaging in the same mice. Mice were head-fixed to a custom freely moving disk that allows for natural behaviors such as walking and grooming. We performed awake mesoscopic Ca^{2+} imaging (7 mm x 7 mm field of view, 20 Hz, 340 x 340 pixel resolution) of the dorsal cerebral cortex during spontaneous natural behaviors. High-speed infrared cameras recorded the behaviors simultaneously with the brain imaging, and limb movements were tracked using DeepLabCut, a machine learning algorithm. To assess changes in widespread cortical function, we first used spatial independent component analysis (ICA, SOBI and JADE algorithms) to segment the Ca^{2+} imaging data into functional independent components (ICs) in control mice and mice one month after mTBI. The data was separated into 1 min blocks for the analysis. The number, stability, and frequency of occurrence of ICs were compared between control and mTBI mice. Preliminary ICA using SOBI revealed a total of 468 unique ICs, 215 found only in control, 162 only following mTBI, and 91 that overlapped between control and mTBI. These ICs were composed of 48 unique domains that covered the majority of the visible dorsal cortical surface, with each IC comprised of 1-4 individual domains. The domains are relatively conserved, with only one domain specific to control mice, and 3 domains specific to mTBI mice. Next, we used both correlation matrix and graph theory approaches to assess changes in network connectivity following mTBI. Initial ICA data using JADE shows a large decrease in functional connectivity between ICs one month after mTBI, as quantified by a reduction in nodal degree (number of significant correlations/node), from an average of 20.3 ± 6.3 to 11.0 ± 3.1. These results suggest that a relatively mild cortical impact produces a chronic decoupling of functional network connectivity that could contribute to behavioral and cognitive dysfunction.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.16/H34

Topic: C.10. Brain Injury and Trauma

Title: The glymphatic function following repetitive mild traumatic brain injury: Risk for Parkinson’s disease?

Authors: *X. CAI[1,4], I. HARDING[1], J. QIAO[2], B. COLARUSSO[4], T. KNOX[4], P. P. KULKARNI[3,4], C. F. FERRIS[3,4];
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Abstract: The glymphatic system (GS), a recently discovered waste clearance system in the brain, is described by the circulation of cerebrospinal fluid along glymphatic pathways penetrating to extracellular space, facilitated by aquaporin-4 (AQP4) water channels, allowing drainage throughout the brain. There is a growing literature that glymphatic system may play a critical role in the etiology and pathophysiology of CNS disorders. For example, recent work has suggested that the GS is largely impaired by 60% in moderate-to-severe traumatic brain injury (TBI). However, mild TBI (mTBI) characterized as a negligible loss of consciousness with minimal neuropathology is estimated to account for 75% of all TBI cases. While mTBI is difficult to detect, it causes chronic damage to the brain especially when exposed to repeated concussion, contributing to cognitive, motor and behavioral problems with an increased risk for Parkinson's disease. To date, little is known regarding how repetitive mild traumatic brain injury (rmTBI) impairs GS. This study aims to test the hypothesis that rmTBI causes reduced glymphatic flow(GF) in the midbrain dopaminergic system, altering AQP4 expression and localization in the perivascular domain, and reducing clearance efficiency in alpha-synuclein, a harmful protein forming Lewy bodies. Contrast-enhanced MRI experiments were performed through intracerebroventricular injection to follow brain-wide contrast agent dynamics over 2hs along the glymphatic pathway on fully awake rats exposed to rmTBI rats (n=7) as compared to non-concussed controls (n=7). TBI rats were hit on the forehead twice (48 hrs interval) with 7.4 m/s impact velocities and 30 psi based on momentum exchange model, three weeks prior to imaging. Behavior assays including Novel Object Preference and Barnes Maze were conducted to evaluate cognitive function a week after concussion. Immunohistochemistry on AQP4 co-stained with blood vessels were conducted to assess AQP4 expression/localization in the perivascular domain. Fluorescence conjugated alpha-synuclein proteins were intrastriatally administered in controls and rmTBI animals to assess clearance efficiency longitudinally with fluorescent imaging. Behavior results showed significantly reduced path efficiency in rmTBI rats compared to controls in Barnes Maze, indicating spatial memory deficits following repeated concussion. Altered glymphatic activity observed in the midbrain suggests a possible mechanism between mild head injury and PD that may lead to targeted treatments for neurodegenerative diseases.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.17/H35

Topic: C.10. Brain Injury and Trauma

Support: DOD PR161864

Title: Does treatment with sleep aids following TBI alter the development of post-traumatic epilepsy?

Authors: *P. V. RODRIGUES[1], S. S. R. KONDURU[1], J. A. PFAMMATTER[2], M. V. JONES[3], R. K. MAGANTI[1];
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Abstract: Traumatic Brain injury (TBI) leads to several sequelae including post-traumatic epilepsy (PTE), sleep-wake disturbances (SWD) and even mood disorders. Currently there are no preventive treatments for these sequelae.However, it is well established that lack of sleep triggers seizures, but it is unclear if SWD leads to PTE. We hypothesized that post-TBI SWD is linked to the development of PTE. Here, we aimed to investigate whether sleep aids-dual orexin antagonist (DORA-22) or Gaboxadol (THIP- an agonist of delta subunit containing $GABA_A$ receptor), when used early after TBI, will restore sleep and prevent development of PTE.We performed severe TBI (Controlled cortical impact-CCI) or sham injury (craniotomy only with no injury) in CD-1 mice and implanted epidural EEG electrodes in the right frontal and left parietal areas along with nuchal EMG under isoflurane anesthesia. After TBI/sham injury and EEG implantation animals were treated with either DORA-22, THIP, or control (vehicle control or no treatment) via oral gavage for 1 months from the day of surgery. We then conducted week long video-EEG recordings in week 1, and months 1, 2, 3 and 6. Acquired EEG data was transferred to a sleep scoring software (Sirenia Sleep) and was scored in 4 sec epochs. We then analyzed epileptiform events (seizures and interictal spikes) and sleep-wake patterns across time.Seizures occurred in ~ 25% of TBI animals whether untreated (9/40) or treated (3/12-for DORA-22 and 3/12 for THIP group). Normalized seizure counts (seizures per animal per hour of recording) indicate consistent seizure frequency across time in the untreated TBI animals(1.21 at week 1, 2.78 at month 2, 1.88 at month 3, and 2.08 at month 6). Interestingly, TBI mice treated with DORA-22 has no recorded seizures after the first week (2.78 at week 1and 0 at other time points)and we observed an increase in seizure rate of THIP animals as compared to controls (8.33 at week 1, 4.17 at month 1, 4.69 at month 2, and 0 at month 3). Seizures consisted of behavioral arrest, head nodding and hind limb stretching that sometimes progressed to Racine class V seizures. SWD consisted of “hypersomnia” in the first week, but “insomnia” at month 2

after TBI. Our preliminary results suggest no differences in sleep-wake patterns between DORA-22, THIP, or control treated TBI animals. A full analysis of seizures, interictal spikes (~80% of animals had interictal spikes), and sleep parameters is ongoing and further analysis is focused on understanding relationship between sleep disruptions, epileptiform events with or without treatment.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.18/H36

Topic: C.10. Brain Injury and Trauma

Support: NIH R01-NS101108

Title: Disruption of Sharp wave-Ripple and phase amplitude coupling across laminar hippocampal CA1 following traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is caused by mechanical insults to the head, often resulting in prolonged or permanent brain dysfunction including disruption of cognitive functions. The hippocampus is one of the most studied brain regions following TBI due to its central role in episodic and spatial memory and its demonstrated vulnerability during TBI. Sharp wave-ripples (SPW-Rs) are considered one of the most important hippocampal neural activity patterns that underlie cognitive functions. SPW-Rs are instrumental in stabilizing the spatial representation coded by place cells, refining hippocampal place fields and, by extension, for maintaining a stable cognitive map. Timing of hippocampal CA1 pyramidal cell spikes is tuned by the relative strengths of the cooperating/competing CA3 and entorhinal inputs and the strength of these upstream inputs are reflected by the gamma power in the appropriate lamina of CA1.We hypothesize that TBI may distort the timing of the upstream inputs towards CA1 compromising a proper formation of neuronal ensembles and consequently disrupt the SPW-R generation which may underlie aspects of post-TBI memory dysfunction.Cross-frequency coupling (CFC) and spike-local field potential (LFP) entrainment may support the organization of these neuronal ensembles and are present during a range of cognitive functions, including learning and memory. Using 64-channel silicon probes, we simultaneously recorded laminar hippocampal field structure and CA1 neurons in behaving rats during a familiar-novel

environment paradigm. Recordings were divided into moving and non-moving periods, and then phase-amplitude coupling (PAC) was calculated for every possible pair of channels using the 1-20 Hz band as the phase of the lower frequency oscillation and 1-300 Hz band as the power of the coupled higher frequency oscillation. Results show a reduction in PAC in injured subjects relative to sham, predominantly between radiatum and pyramidal layers in theta-gamma and delta-theta-ripple coupling, thus reflecting a loss of encoding synchrony between CA1-CA3 (low gamma (~30-60 Hz)), EC-CA1 (high gamma (~60-110 Hz)). Moreover, SPW-Rs rate is drastically reduced in injured group in both familiar and novel environments (~50% relative to the sham group), reflecting a reduction of memory retrieval and consolidation events.One interpretation of these results is that laminar afferent inputs into CA1, both from CA3 and entorhinal cortex, are no longer properly coupled to lower frequencies leading to a disruption of neuronal ensembles. In combination with the decrease of SPW-Rs generation, this may affect the proper memory and cognitive functionality.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.19/H37

Topic: C.10. Brain Injury and Trauma

Support: NICHD DP2HD084067

Title: *In vivo* phage biopanning facilitates discovery of acute traumatic brain injury specific targeting peptides

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Abstract: The heterogeneous injury pathophysiology of traumatic brain injury is a barrier to developing highly sensitive and specific diagnostic tools. Thus, biomarker discovery techniques that take advantage of mining this complexity are critical to the identification of biomarkers with high specificity. We employed a unique pipeline for biomarker discovery that entailed domain antibody (dAb) phage display, next generation sequencing (NGS) analysis, and nanotechnology strategies to generate truncated peptide-based motifs. Here we present the results where biopanning was conducted in an acute brain injury mouse model. For *in vivo* phage biopanning, adult C57Bl/6 mice were anesthetized and subjected to either controlled cortical impact (CCI) or sham surgery (n=3 per group/timepoint; approved by ASU IACUC). At 1 day post-injury (dpi), a

dAb phage library was intravenously injected and circulated for 10 minutes. Mice were promptly sacrificed, and phage eluted from injured brain tissue and amplified for a second biopanning round. Truncated peptide sequences were selected from NGS data analysis and developed using nanotechnology strategies. Control peptides were identified from dAb sequences specifically present in peripheral tissue. For validation, serial cryosections (20 µm) were collected from CCI or sham surgery mice at 1 (acute) or 7 (subacute) dpi. Immunostaining consisted of the biotinylated targeting or control peptides serving as a primary "antibody" followed by fluorescently-labeled streptavidin. NGS analysis revealed two select dAbs that were substantially enriched between biopanning rounds within the injury penumbra and not found in control libraries. Two truncated peptide sequences derived from the enriched dAbs, reflective of the unique dAb sequences, were generated to evaluate the specificity to acute neural injury via IHC. Only one peptide demonstrated notable positive recognition of the cortical injury penumbra at 1 dpi while no signal was observed in sham tissues. Furthermore, when testing this peptide on subacute tissue, no positive signal was observed. Negative control peptides did not bind to either injured or sham tissue, suggesting specificity of the injury targeting peptide. The pipeline of phage display followed by NGS analysis demonstrated a unique approach to discover motifs that are sensitive to the heterogeneous and diverse pathology present in neural injury. We successfully identified a unique motif that spatially homes to acute neural injury. Future studies will include immunoprecipitation mass spectrometry experiments to determine the specific antigen targets.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.20/H38

Topic: C.10. Brain Injury and Trauma

Support: DOD Grant PR161864

Title: Sleep spindles and its role as a potential biomarker for the development of secondary epilepsy post traumatic brain injury

Authors: *S. KONDURU, J. PFAMMATTER, P. RODRIGUES, M. JONES, R. MAGANTI; Univ. of Wisconsin - Madison, Madison, WI

Abstract: Epidemiological data shows that post-traumatic epilepsy (PTE) is seen in about 10-20% of patients with Traumatic Brain Injury(TBI). It can be as high as 50% in injured military personnel. Currently, it is uncertain as to who develops PTE after TBI. Sleep-Wake disturbances

are very common in TBI patients and there is a close relationship between sleep disorders and seizures. Here, we analyzed sleep spindles,(a hallmark of NREM sleep) in mouse models of TBI as a potential biomarker for the development of PTE.
We analyzed EEG data sets from 3 cohorts of CD-1mice. 1) TBI cohort (n=40) underwent severe TBI (controlled cortical impact) to the right parietal lobe. 2) Sham cohort (n=22) underwent craniotomy without TBI. TBI and sham cohorts were recorded at week 1, month 1,2,3,6 after surgery. 3) The third set of mice underwent surgery without craniotomy (n= 6). EEG was obtained at week 1 from this cohort to determine the baseline for CD-1 mice. All the obtained EEG signals were 1) Manually scored for sleep-wake patterns in 4s epochs (Sirenia sleep) and artifactual EEG was excluded 2) Manually scored for sleep spindles after bandpass filtering between 9- 15hz (1hour NREM segments) to compare with automated method. 3) TBI cohort manually scored for seizures (Natus Neuroworks). We used an automated spindle detection method based on Ferrarelli et al(2007) in Wonambi, Python. Automated analysis was done using multiple detection and selection thresholds and correlated with manual spindle scoring. The best possible match (~50%) was identified when the detection and selection thresholds were set to 3 and 2. The method will be further reviewed and validated to yield higher predictive value and F1 score. Other parameters used for spindle detection are frequency (9-15hz) and duration(0.5-2s). We compared spindle results from validated automated detection across groups, TBI with seizures (~25% of TBI recorded), TBI without seizures and Sham. Preliminary analysis showed a difference in mean peak amplitude and power between sham (108.35+/-28.06; 10.43+/-4.74) and TBI groups (84.95+/-17.39; 6.67+/-2.59). Within the TBI groups, there was no difference in average peak amplitude and power between TBI animals with seizures (84.99+/-23.96; 6.37+/-3.26) and TBI animals without seizures (84.91+/-10.82; 6.97+/- 1.92). Normalized spindle density/hour/animal showed an increase in spindle density in TBI animals with seizures (47.58) and TBI animals without seizures (43.24) compared to sham (25.23). There was no difference in the mean frequency(hz) and duration of the spindles(sec) across groups. Further analysis of our data is being done to determine the significance of these findings.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: C.10. Brain Injury and Trauma

Support: CONACyT GRANT No. 575264
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Title: Characterization of dendritic spines, synaptophyisin and α-Synuclein in the orbitofrontal cortex tissue from suicide victims

Authors: *A. J. VAZQUEZ HERNANDEZ[1], A. A. ORDUÑA[2], L. ARROYO GARCÍA, SR[3], R. A. VAZQUEZ, SR[4], H. TENDILLA[5], S. DURAN[6], F. TAKAJASHI MEDINA[7], F. GARCIA-DOLORES[8], G. FLORES[9];
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Abstract: According to the statistics of the World Health Organization (WHO) about one million people commit suicide annually in the world, so it reaches a remarkable thirteenth place as cause of death. Suicide is a mental illness that can occur at any age, it is a behavior determined by a large number of complex causes, mainly depression and alcohol use disorders, substance abuse, violence and various cultural and social environments becoming in a public health problem that need to be studied. The prefrontal cortex (PFC) is functionally related to emotion, stress and cognitive functions, aspects involved in suicidal behavior. The lesions of the prefrontal cortex entail a certain loss of decision capacity, so it is possible that alterations in this region lead to the inability to make appropriate decisions. The dendritic spines are dendritic membrane modifications, whose morphology changes could suggest modifications in neural communication, also this changes in their morphology and spines density are associated with several pathologies. In this work we aim to describe the morphological modifications of dendritic spines in the PFC, specifically in the orbitofrontal cortex of human tissue samples we obtained at forensic autopsies, with informed consent and according to an institutional approved protocol. Coupled with this we measured levels of synaptophysin, this glycoprotein has an important function in the exocytosis of synaptic vesicles in neurons, and therefore a generalized marker of synapses. Likewise, we aimed to measure the concentration of α-synuclein (α -Syn), which is a nuclear and synaptic protein and it is the main component of Lewy bodies in some neurodegenerative pathologies. In addition, to the samples of suicide victims, we obtained samples of patients who died from other causes, with the aim of having a “control group”. With these two groups, we created another 2 subgroups, which were "young group" (13-29 years old) and "adult group" (31-65 years old). It should be noted that the information known about all the samples was the cause of death, age and gender. Our results suggest that suicide victims have a modification in dendritic spine morphology, a decrease in dendritic spine density that could be related to the decrease in synaptophysin levels that we found. In other hand, our results suggest α -Syn does not show significant changes. It is known PFC is critically involved in emotional and cognitive processes, the activity of this cerebral area could be a biomarker for this psychopathology, thus, post-mortem findings seem to illustrate a pathophysiological condition predisposing to the suicidal episode, follow-up could be useful for the prevention of suicide.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.22/H40

Topic: C.10. Brain Injury and Trauma

Support: NCTR/FDA protocol E0766001

Title: *In vitro* simulated traumatic brain injury decreases tyrosine hydroxylase expression in human primary dopaminergic cells

Authors: *M. A. RAMIREZ-LEE, Sr, H. ROSAS-HERNANDEZ, S. M. LANTZ, E. CUEVAS, S. F. ALI, S. Z. IMAM;
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Abstract: A large number of Americans live with traumatic brain injury (TBI)-related disabilities. TBI occurs when external mechanical forces cause tissue deformation sufficient to induce brain damage. One of the hallmarks of TBI is neuronal death, but it is related to the development of neurodegenerative disorders, including Parkinson's disease (PD). In PD, the loss of dopaminergic neurons as well as decreased tyrosine hydroxylase (TH) expression and activity contribute to dopaminergic dysfunction. The precise link between TBI and the development of PD is not known, but it has been hypothesized that the decrease in TH expression and activity may be contributing factors. However, it remains unclear if TBI worsens the neurodegeneration observed in PD. Here, we evaluated the effects of in vitro simulated TBI on TH expression. To model PD, human primary dopaminergic neurons were treated with 1 mM methyl phenylpyridinium ion (MPP^+) for 24 hours. To simulate TBI, control and MPP^+-treated neurons were subjected to 0%, 10%, 25% and 50% biaxial stretch deformation. TH protein expression was evaluated 1, 2, 7 and 14 days after injury. As expected, MPP^+ decreased TH expression at all time points, successfully modeling dopaminergic dysfunction observed in PD. In addition, TH expression decreased after 10, 25 and 50% of stretch at measured time points; however, this effect occurred only in control cells, not in MPP^+-treated cells. Our data suggest that TBI promotes PD-like dopaminergic dysfunction, but does not exacerbate the damage already observed in the PD in vitro model. These data also suggest that both, TBI and PD may have similar mechanisms of damage involving the expression and activity of TH. Further studies are underway analyzing additional mechanisms of dopaminergic toxicity.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: C.10. Brain Injury and Trauma

Support: R21NS098129

Title: The influence of the val66met polymorphism of the brain derived neurotrophic factor gene on pathology in an isogenic human *in vitro* model of neurotrauma

Authors: C. K. FRANZ[1], J. K. PHILLIPS[2], K. Y. COTTON[1], J. GRAFMAN[3], M. J. QUEZADA[1], ***J. D. FINAN**[2];
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Abstract: Traumatic brain injury (TBI) outcomes vary widely between patients - even when patients have a similar severity of injury. Common, genetic variants cause some of this variation, but well-designed human experimental studies of the effects of genetic predisposition on TBI outcome are both rare and have obvious ethical limitations. Human in vitro models address these limitations. Human-origin neurons can be generated from human subjects for culture in vitro using induced pluripotent stem cell technology. These neurons can be genetically edited to create isogenic neurons i.e. neuron populations that differ by only one genetic variant. This study used isogenic neuron populations to study the influence of the val66met polymorphism of the brain-derived neurotrophic factor (BDNF) gene on neurotrauma pathology. Isogenic induced pluripotent stem cells carrying the 3 genotypes of this polymorphism (val/val, val/met or met/met) were differentiated into excitatory, cortical neurons. They were then cultured at 60,000 cells/cm^2 on silicone membranes for 48 hours before stretch injury. Cells were injured with a 28% biaxial stretch pulse lasting 30 ms. Differentiated neurons expressed green fluorescent protein. 4 hours after injury, they were stained with 5 μg/ml Hoechst 33342 to label nuclei and then fluorescently imaged. These images were analyzed to quantify neurite outgrowth. Trauma significantly reduced mean neurite outgrowth per cell. There was also a significant effect of genotype on mean neurite outgrowth per cell and a significant interaction between the effect of trauma and the effect of genotype (2 factor ANOVA, $p< 0.05$). These results show that in vitro neurotrauma experiments in human isogenic cells can isolate the influence of a genetic variant on neurotrauma outcomes. They therefore offer a powerful opportunity to explore the association between genotype and neurotrauma morbidity that continue to be reported in large-scale clinical

TBI studies. The resulting insights could inform efforts to personalize therapy, stratify clinical trials and assess patient-specific susceptibility to poorer outcomes after neurotrauma.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.24/H42

Topic: C.10. Brain Injury and Trauma

Support: Indiana State Department of Health's Indiana Spinal Cord and Brain Injury Research Fund
CDMRP W81XWH1810433

Title: The influence of mild traumatic brain injury on immune response and development of post-traumatic headache in healthy adults

Authors: J. A. SMITH[1], J. XIE[2], P. MALICKY[2], C. CAREY[4], J. M. SAXE[5], K. M. NAUGLE[4], ***F. A. WHITE**[2,3];
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Abstract: Post-traumatic headache (PTH) is one of the most common and persistent symptoms following mild traumatic brain injury (mTBI), often disrupting recovery in civilian/military populations. PTH has to date no defining clinical features, and is subsequently classified as a secondary headache disorder. While PTH can be transient, some patients go on to experience long-term PTH as evidenced by daily or several times a week attacks of headache pain. Despite the prevalence of PTH following mTBI, the pathological mechanisms underlying the development of chronic PTH's remain poorly understood. Research now suggests that monocytic cell subpopulations have an underappreciated role in the evolution of mTBI-associated PTH and may contribute to both subacute and chronic PTH sequelae. To investigate potential contributions of monocytes, we examined the major subpopulations of human monocytes. These cell populations are divided into high CD14 but no CD16 expression (CD14+CD16−) termed classical monocytes. An intermediate subset consists of high CD16 and high CD14 (CD14+CD16+) and a nonclassical subset as high CD16 but with relatively lower CD14 expression (CD14lowCD16+). Importantly, these cell subpopulations are known to preferentially transmigrate across the blood brain barrier and may contribute to neuroinflammation. The aim of this study is to prospectively determine the preponderance of the different monocyte

subpopulations in mTBI patients for up to 4 months post-injury. Adult mTBI patients recruited from Level I Emergency Department Trauma Centers completed study sessions at 1-week, 1-month (sub-acute), and 4-months (chronic) post mTBI (n=31). Participants completed a health history questionnaire, psychological questionnaires (Pain Catastrophizing Scale, Center for Epidemiological Studies – Depression Scale), and a headache survey which included a 0-10 numeric pain rating scale (NRS) to measure average intensity of headache pain. Additional assays included quantitative sensory tests which were administered to participants to measure endogenous pain modulation. The biological methods used to conduct this study were flow cytometry and LPS stimulation of peripheral blood mononuclear cells followed by cytokine/chemokine quantification. Currently, experiments concerning monocyte subpopulations and cytokine secretion following LPS stimulation are ongoing. Our data to date suggests substantial dynamics in monocyte subset distributions over the 4-month time period which could contribute to the clinical outcomes of PTH pain and depression and may serve as biomarkers or as potential therapeutic targets.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

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Topic: C.10. Brain Injury and Trauma

Support: Indiana State Department of Health's Indiana Spinal Cord and Brain Injury Fund Research Grant Program
St. Vincent Foundation

Title: The role of deficient pain modulatory systems in the development of subacute and chronic post-traumatic headaches following mild traumatic brain injury: An exploratory study

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Abstract: Post-traumatic headache (PTH) is one of the most common and persistent symptoms following mild traumatic brain injury (mTBI), often disrupting recovery in civilian and military populations. Despite the high prevalence of PTH following mTBI, the pathological mechanisms underlying the development of chronic PTH's remain poorly understood. Recent animal and cross-sectional human studies indicate that mTBI may exert deleterious effects of endogenous

pain modulatory function, potentially underlying the elevated risk for intense and chronic PTH's following injury. Thus, the primary purpose of this prospective pilot study was to evaluate whether early pain modulatory profiles (sensitization and endogenous pain inhibitory capacity) after mTBI predicted the development of PTH's sub-acutely and chronically in mTBI patients. Adult mTBI patients recruited from Level I Emergency Department Trauma Centers completed study sessions at 1-week, 1 month (sub-acute), and 4-months (chronic) post mTBI (n=31). During each session quantitative sensory tests were administered to participants to measure endogenous pain modulatory function including 1) the conditioned pain modulation (CPM) test to measure endogenous pain inhibitory capacity and 2) temporal summation of pain test and pressure pain thresholds (PPT's) of the head to measure sensitization of the head. Participants also completed a health history questionnaire, psychological questionnaires (Pain Catastrophizing Scale, Center for Epidemiological Studies - Depression Scale), and a headache survey which included a 0-10 numeric pain rating scale (NRS) to measure average intensity of headache pain. Hierarchical regression analyses were used to predict headache pain intensity at 1-month and 4-months post injury, with potential predictors including demographic variables and outcome measures assessed at 1-week post injury. The regression for sub-acute headaches indicated that after controlling for headache pain at 1 week post injury, PPT's of the head ($p=.023$; $\beta=-0.36$) predicted headache pain at 1-month. For chronic PTH's, the results indicated that headache pain at 1-week ($p=.009$; $\beta=.39$), pain catastrophizing score ($p=.013$, $\beta=0.375$), and pain inhibitory capacity on the CPM test ($p=.023$, $\beta=-0.34$) predicted headache pain at 4 months, account for 51% of the variance. These results suggest that pain sensitization of the head is a risk factor for sub-acute PTH's, while deficient pain inhibitory capacity and pain catastrophizing early after a mTBI are risk factors for chronic PTH's.

Disclosures: K.M. Naugle: None. **C. Carey:** None. **J. Hackett:** None. **J. Saxe:** None. **F.A. White:** None.

Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.26/H44

Topic: C.10. Brain Injury and Trauma

Support: NIH Grant UH3NS095554

Title: Alpha modulation during rest and vigilance and autobiographical memory retrieval tasks in the human central thalamus

Authors: *E. Y. CHOI[1], J. L. BAKER[3], A. S. FOGARTY[4], D. T. AVANSINO[1], A. P. JANSON[5], B. K. RUTT[2], C. R. BUTSON[5], N. D. SCHIFF[3], J. M. HENDERSON[1]; [1]Neurosurg., [2]Radiology, Stanford Univ., Stanford, CA; [3]Feil Family Brain and Mind Res. Inst.,

Weill Cornell Med. Col., New York, NY; [4]Stanford Hlth. Care, Palo Alto, CA; [5]Biomed. Engin., Univ. of Utah, Salt Lake City, UT

Abstract: Human neuroimaging and non-human primate neurophysiology studies demonstrate the role of the central thalamus in arousal regulation and executive function1,2. However, a direct human neurophysiological signature of the central thalamus's contribution to these functions has yet to be reported. Here, we report the first observation of an enhancement of ~10Hz alpha power in the human central thalamus during different rest conditions, a variable-delay visually-guided saccade task ("vigilance task"), and an autobiographical memory (AM) retrieval task. A 40-year-old female patient with a moderate-to-severe traumatic brain injury (msTBI) was bilaterally implanted with Activa PC+S (Medtronic) deep brain stimulation (DBS) electrodes in the central thalamus, allowing both stimulation and recording of local field potentials (LFPs). Post treatment phase, LFPs were recorded from the top- and bottom-most contacts of each electrode as the patient was at rest with eyes closed, eyes open free viewing, or eyes open fixating. Power spectral density (PSD) estimates showed state-dependent modulations in mean power in the 7-12Hz alpha band in the right electrode. Recordings were also taken while the patient performed interleaved blocks of a saccade task with a variable fixation vigilance period and of a word-cued AM task in which the patient pressed a button upon successfully retrieving a memory. PSD estimates showed small modulations in mean power at ~5Hz theta and ~15Hz beta frequencies in the saccade versus vigilance epochs of the vigilance task (n=92). A robust modulation of ~10Hz alpha power was observed in the AM task (n=33) after the button press indication of a memory retrieved. These preliminary results demonstrate the first potential neurophysiological markers of arousal in the human central thalamus, with potential roles in vigilance, eye movement, and AM retrieval.

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Poster

479. Traumatic Brain Injury: Mechanisms, Biomarkers, and Recovery

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 479.27/H45

Topic: C.10. Brain Injury and Trauma

Support: VA I01BX004312
Diversity Supplment - Parent Grant R01AG058252

Title: Assessing biomarker potential and cytotoxicity of neuronal and astrocyte derived exosomes from individuals with mild traumatic brain injury

Authors: *C. N. W. WINSTON[1], R. A. RISSMAN[2], V. B. RISBROUGH[3];
[1]UC San Diego, LA Jolla, CA; [2]Neurosci, UCSD Sch. of Med., La Jolla, CA; [3]Dept. Psychiatry, Univ. of California San Diego, La Jolla, CA

Abstract: The prevalence of TBI is high, but to-date it is difficult to diagnose; there is currently no diagnostic biomarker, in particular, for mild TBI (mTBI) with persistent post concussive symptoms. To examine the potential of neuronally - derived (NDE) and astrocytic-derived (ADE) exosome cargo proteins as biomarkers of chronic mTBI in younger adults, we examined plasma exosomes from combat-deployed Marine and Navy service personnel enrolled in a prospective longitudinal study of combat-related risk and resilience, Marine Resiliency Study II (MRSII). We focused on blood samples collected from participants that self-reported at >1 mTBI while on deployment [MOU1] (mean age, 21.7 ± 0.2), and age-matched, controls (deployed service members that did not endorse a deployment-related TBI or a history of TBI; mean age, 21.95 ± 0.3). Plasma exosomes were precipitated and enriched against a neuronal adhesion protein, L1-CAM, and an astrocyte marker, glutamine aspartate transporter (GLAST) using magnetic beads to immunocapture the proteins and subsequently selected by fluorescent activated cell sorting (FACS). Extracted protein cargo from NDE and ADE preparations were quantified for protein levels implicated in TBI neuropathology by standard ELISAs and on the ultra-sensitive Single molecule assay (Simoa) platform. Plasma NDE and ADE levels of Aβ42 were significantly higher while plasma NDE and ADE levels of the postsynaptic protein, neurogranin (NRGN) were significantly lower in participants endorsing mTBI compared to controls with no TBI history. Plasma NDE levels of Aβ40, total tau, and neurofilament light (NFL), P-T181-tau, P-S396-tau, were not significantly different between the two patient populations. Plasma ADE levels of P-T181-tau and P-S396-tau were not significantly different between mTBI and control samples. Lastly, plasma NDE but not ADE cargo proteins from mTBI samples were found to be toxic to neuron-like recipient cells *in vitro*.

Disclosures: C.N.W. Winston: None. **R.A. Rissman:** None. **V.B. Risbrough:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.01/H46

Topic: C.10. Brain Injury and Trauma

Title: Upper alpha to theta ratio predicts duration of post traumatic amnesia following traumatic brain injury

Authors: *M. L. VINAO-CARL, N. GORGORAPTIS, D. J. SHARP;
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Abstract: PTA is a transient neurological disorder characterised by marked retrograde amnesia following traumatic brain injury (TBI). Structural damage to white matter tracts known as diffuse axonal injury (DAI) disrupts large-scale connectivity and hampers integration and consolidation of information within functional brain networks. However, the electrophysiological substrates of this altered connectivity remain poorly understood. EEG offers excellent temporal and spectral resolution for the analysis of neuronal oscillatory processes, an intrinsic property of resting state networks. To investigate network connectivity inverse modelling of alpha and theta rhythms was implemented through DICS and PCC beamformers. Spectral analysis and source reconstruction was conducted within individual frequency bands due to distortions in frequency architecture within PTA subjects. Graph theory indices of coherence were used to compare changes in network topology between controls (n = 13), acute PTA subjects (n = 11) and PTA subjects at follow up (n = 5). Power analysis in channel space revealed a net increase in theta and decrease in alpha power in acute PTA. Source reconstruction confirmed attenuated of alpha within key nodes of the dorsal attention network (DAN), cingulo-insular thalamic system (CITS) and default mode network (DMN). Conversely theta power was abnormally high across multiple networks and co-localised with reductions in alpha power, most notably in medial temporal lobe structures. In acute PTA, we observed an increase in upper alpha to theta ratio (UATR) compared to lower alpha to theta ratio (LATR), while the opposite was true at follow-up. Additionally, UATR but not LATR or TATR correlated with PTA duration. Contrary to expectation total alpha to theta ratio (TATR) was higher than controls at follow-up while theta power normalised, suggestive of a divergent contribution of theta and alpha to acute and long-term PTA deficits. Graph theory analysis based on coherence compounded these findings by revealing chronic disorganisation of alpha and theta connectivity throughout mnemonic and attentional networks which normalised at follow-up. We hypothesise that the slowing of alpha and theta rhythms reflects changes in connectivity from DAI induced deafferentation resulting in a shift in global frequency architecture. We provide evidence that theta and alpha rhythms though propagating through homophilous networks make distinct contributions towards the symptomatology of PTA.
<!--EndFragment-->

Disclosures: **M.L. Vinao-Carl:** None. **N. Gorgoraptis:** None. **D.J. Sharp:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.02/I1

Topic: C.10. Brain Injury and Trauma

Title: The impact of subconcussive head injuries on cognition-linked electrophysiological markers in contact sport athletes

Authors: *N. M. RASO[1], M. MAZUREK[1], S. BECKER[2], I. KINLEY[2], L. IAFRATE[2], C. PIRES[2];
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Abstract: Concussion is a form of mild traumatic brain injury (mTBI). Sport-related concussions are some of the most common and significant injuries sustained by athletes, and are often accompanied by psychological sequelae such as impaired memory and attention. Recently, attention has been paid to potential cognitive effects of repetitive subconcussive head injuries (RSHI) which may result during contact sport participation in the absence of a sustained concussion. Changes in local spectral power on electroencephalography (EEG), particularly peak alpha frequency (PAF) slowing, have been reported in concussions and mTBI (Dunkley 2015). PAF has been shown to differentiate groups of adults with higher memory performance from those of lower performance, groups of children with advanced reading ability from matched controls, and to predict state-dependent working memory (Angelakis 2004). To our knowledge changes in local spectral power have not been specifically examined in a population that is sustaining RSHI. We initially assessed 35 male high impact university rugby players ages 18-21 three times during the course of their season (t1: pre-contact season, t2: mid-season [5 weeks after contact initiated], and t3: end-season [8 weeks after contact initiated]). At each time point, they underwent 5 minutes of eyes-closed resting state EEG using the Cognionics Quick-20 dry electrode EEG headset. We hypothesized that over the course of a season athletes would demonstrate lower PAF, when controlling for concussion. Abnormal EEG findings have also been reported in athletes with a remote history of concussion, thus we expected baseline PAF to be negatively correlated with prior concussive injuries. We observed PAF slowing from t1 to t2 ($p = 0.016$ two-sided), with no significant change from t2 to t3 ($p = 0.512$ two-sided). These changes coincided with the highest intensity of expected impact throughout the rugby season, suggesting a relationship between RSHI and PAF. We also observed a negative correlation between PAF and self-reported number of RSHI, specifically participants' response to how many times they had their "bell rung" (colloquial phrasing for cranial impact; $p = 0.02$ controlling for concussions). Interestingly, the same trend was not observed when asked about "hard hits" or "concussion." This reporting difference may be due to stigma or concern about athletic sequelae of reporting head injuries as "concussions." These results overall are suggestive of a possible link between repeated subconcussive cranial impact and impaired electrophysiological markers of cognitive function.

Disclosures: **N.M. Raso:** None. **M. Mazurek:** None. **S. Becker:** None. **I. Kinley:** None. **L. Iafrate:** None. **C. Pires:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.03/I2

Topic: C.10. Brain Injury and Trauma

Title: Patterns of binocular horizontal and vertical saccade velocity abnormalities in mild TBI

Authors: *J. H. ANDERSON;
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Abstract: Mild traumatic brain injury (mTBI) can result in significant problems affecting vision and oculomotor function (Armstrong, 2018), vergence eye movements (Magone et al., 2014; Suhr et al., 2015), spatial orientation, movement, and balance (Wallace and Lifshitz, 2016; Hoffer et al., 2010), These issues can result in problems with gaze control, eye-head-coordination, and visual-motor transformations underlying goal-directed movements. This can occur after multiple head trauma events, and in some cases after a single mild TBI event. Also, symptoms can persist years after the original trauma (Danna-Dos-Santos et al., 2018) and can become progressively worse over time. Effects of the natural aging processes probably interact with the pathophysiology resulting from TBI. This ongoing research is part of an effort to evaluate oculomotor function (saccades and pursuit eye tracking) during binocular viewing in mTBI. The general aims are to characterize the coordinated movement of the two eyes during changes in gaze in response to movement of a visual target (e.g., during saccades and visual pursuit of an object in three dimensional space) and during attempted visual fixation when there is head movement, to compare the eye velocity profiles of the two eyes in the presence of convergence, and to relate the velocity trajectories of the two eyes to vergence dysfunction in mTBI. For this study, the horizontal/vertical position and velocity of the left eye versus the right eye were analyzed. Saccade targets were presented 5 to 25 degrees left/right of center, 5 to 15 degrees above/below center, and 10 to 15 degrees diagonally from center. Plots of left versus right horizontal eye velocity and vertical versus horizontal eye velocity were quantified with polynomial regressions of eye velocity toward and away from zero velocity. Cluster and discriminant analyses of the regression coefficients identified those subjects with abnormal velocity trajectories. Some patterns included the following. For large saccade amplitudes there could be different velocities for the adducting eye versus the abducting eye in mTBI subjects who have convergence insufficiency or convergence excess. Furthermore, there could be a velocity asymmetry for rightward versus leftward saccades. These preliminary results have identified eye velocity patterns that show promise for characterizing binocular eye movements in mTBI. Further work will evaluate gaze in three dimensions where there are changes in vergence. The results could provide further insight into the underlying pathophysiology affecting the control of gaze in mTBI and suggest possibilities for evaluating vision therapy.

Disclosures: **J.H. Anderson:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.04/I3

Topic: C.10. Brain Injury and Trauma

Support: Department of Defense W81XWH-16-2-0020

Title: Slow potentials of spreading depolarizations in clinical electrocorticography of traumatic brain injury: Measurement and modeling

Authors: T. WATANABE[1], ***J. A. HARTINGS**[2];
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Abstract: Spreading depolarizations (SDs) are a primary mechanism of lesion development in stroke and brain trauma. In extracellular micropipette recordings using a salt bridge and DC amplifier, they are recorded as a propagating (2-9 mm/min), large (up to 20 mV), negative DC shift, reflecting electrical sources and sinks of mass tissue depolarization. In clinical monitoring of patients, by contrast, SDs are recorded by subdural electrocorticography (ECoG) from platinum macroelectrodes, and DC waveforms are more variable, longer-lasting, and multiphasic than those recorded with laboratory techniques. Here we describe and model the DC waveforms of SDs in clinical recordings as a first step to understanding their physiologic basis. Continuous DC-ECoG recordings (median 72 hr) were obtained from 19 patients during neurointensive care after placement of subdural 6-contact electrode strips during neurosurgery for treatment of severe brain trauma. In expert visual review, 1,050 unique SD wavefronts were identified and yielded 2,904 unique recordings of SD on different electrodes. Semi-automated methods were used to measure SD waveforms after correcting for baseline drift. The negative DC shift had an amplitude of 3.35 mV (median; 5-95% range: 0.53-11.15) and duration of 155 sec (5-95%: 67-295), and was often followed by a prominent positivity. The positivity amplitude was 0.97 mV (5-95%: 0.30-3.92 mV) and the duration was 222 sec (5-95%: 69-735). The delay between positive and negative peaks was 142 sec (5-95%: 70-758). All measures were non-normally distributed, and amplitude distributions were multimodal. Waveforms were then modeled under the assumption that potentials reflect the sum of two competing, partially overlapping processes [-N(t) and P(t)] that drive the ECoG voltage [V(t)] in opposite directions: $V(t) = -N(t) + P(t) + e(t) + s(t)$, where e(t) is an error term corresponding to very low frequency activity, and s(t) is the DC trend. N and P were each modeled as the product of two logistic sigmoidal functions with different rise, peak, and decay parameters, with an offset between initiation times. The model robustly fit all waveforms and captured extreme, unexplained variations in morphology. These results suggest the hypothesis that the morphological heterogeneity of SDs can be explained as

variations in two competing physiologic processes that influence the recorded DC potential. While the nature of these processes has not been determined, we speculate the involvement of blood flow responses to depolarization and the sensitivity of platinum electrodes to affected molecular species.

Disclosures: T. Watanabe: None. **J.A. Hartings:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.05/I4

Topic: C.10. Brain Injury and Trauma

Support: ERA-NET NEURON grant from the National Centre for Research and Development (ERA-NET-NEURON/17/2017)
Hannelore Kohl Foundation Award

Title: Large-scale receptor tyrosine kinase screening reveals dynamic signaling architecture; unveiling novel translational targets for therapy in blunt traumatic brain injury at acute time point

Authors: *R. REHMAN[1], M. MILLER[3], M. MULAW[2], A. CHANDRASEKAR[4], U. HASSAN[5], A. TAKEOKA[3], F. ROSELLI[1];
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Abstract: Traumatic Brain Injury (TBI) is a highly complicated pathology involving multiple events occurring simultaneously including, but not limited to, inflammation, blood brain barrier disruption, apoptosis and alterations in neuronal signaling. Due to limited understanding of complex protein interactions and therapeutic explorations so far in TBI, we focus on mapping large scale signaling architecture originating from key regulators of multiple signaling events (such as cell proliferation, differentiation, apoptosis); Receptor Tyrosine Kinases (RTKs), at therapeutically effective time point. We opted for an advanced unbiased approach to explore the spatial (cellular specificity) and temporal dynamics (control, 3 hours, 24 hours, 3 days and 7 days) of 14 different RTK families post TBI in wild-type B6SJL male mice, aged P60-P80 (n= 6/group). Based on Linear Models for Microarray and RNA-Seq Data (LIMMA) analysis (R software package) on protein expression, our initial investigation of temporal activation revealed that most signaling events initiate at 3-hours post-TBI, limiting our therapeutic window. After establishing the temporal significance and spatial relevance (histological evidence) of RTKs with therapeutic insight, we performed a large-scale in-depth analysis of 223 different tyrosine kinase proteins and identified activated signaling proteins that showed significant differences compared

to the control group to identify distinct signaling modules (n=4/ group). To explore the therapeutic significance of selected signaling modules (phosphorylated C-met, phosphorylated Btk and phosphorylated VEGFR1), we orally administered single dose of FDA approved (to ensure translational effectivity) RTK inhibitors (JNJ38877605 Medchem; specific inhibitor for p-Cmet - 40mg/kg, CC292 Selleckchem; specific Inhibitor against p-btk - 30mg/kg, and PTK787 Selleckchem; specific inhibitor for p-VEGFR 2 & 1 - 50mg/kg) 2 hours (time until reaches maximum receptor occupancy in brain) before trauma. Inhibiting p-Cmet and p-VEGFR1 revealed alteration in the downstream signaling and partial signaling convergence. Post inhibition behavioral analysis of pellet retrieval task revealed improvement in cognitive performance and motor recovery after single inhibitor treatment post trauma (n=4 per group). Prolonged treatment (starting 2 hours pre-TBI until 7 days, one dose/day) of p-Cmet inhibitor revealed significant behavioral improvement until withdrawal of inhibitor treatment (n=5). We conclude that pathological outcome can be mitigated as early as 1-day post TBI by signal specific RTK treatment during therapeutically effective time window.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.06/I5

Topic: C.10. Brain Injury and Trauma

Support: NIH grant RO1NS089901

Title: Elevating microRNA-125b to treat traumatic brain injury via multiple target genes in rats

Authors: *B. G. LYETH[1], X. CHENG[2], Z. YE[4], B. LYU[3], T. OMUNGUYE-GEORGE[3], D. LIU[3];
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Abstract: Our pilot miRNA expression study demonstrated that miR-125b is significantly decreased in blood as early as 3 hr and the decrease lasts for at least 14 days after lateral fluid percussion induced traumatic brain injury (TBI) in rats. It was recently reported that miR-125b is decreased in blood of military combat veterans with post-traumatic stress disorder (PTSD).
In this study, we hypothesized that miR-125b mimic improves outcome after TBI. Using experimental TBI models, our data show that miR-125b mimic (2.4 mg/kg, i.v. and i.c.v.) blocks leukocyte infiltration, reduces cognitive deficits, and decreases neuronal death in hippocampus after TBI. Our miR-125b targetome studies show that a set of miR-125b target genes (Mknk2,

Alkk3, Neu1, others) are responsible for the therapeutic efficacy of miR-125b mimic on TBI. The preliminary mechanistic study data show: 1) miR-125b binds to the 3' untranslated regions (3'UTR) of Mknk2 and Neu1; and 2) Morpholino Oligos (MOs)-miR125b-Mknk2 acts like antagonists to block the binding of miR-125 to 3'UTR of Mknk2. Our ongoing study is to determine whether MO-miR125b-Mknk2/Alpk3/Neu1 *in vivo* prevents miR-125b mimic-induced decrease of these target genes in blood cells (leucocytes, platelets), endothelium, and brain cells (neurons, astrocytes, microglia) after TBI in rats, and thus blocks the therapeutic effects produced by miR-125b mimic after TBI.
In summary, this experiment tested whether miR-125b mimic has both peripheral and central effects to improve TBI outcome via decreasing miR-125b target oncogenes/kinases (Mknk2, Alpk3, Neu1). The combined use of i.v. miR-125b mimic and liposomes to treat TBI in rats is novel, and can be translated to treat human TBI. Our future studies will determine if the long-term decrease of miR-125b in blood is associated with the progression of PTSD after TBI.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.07/I6

Topic: C.10. Brain Injury and Trauma

Title: Ketogenic diet ameliorates cognitive impairment in a mouse model of TBI

Authors: M. HAR EVEN[1], V. RUBOVITCH[1], S. SCHREIBER[2], ***C. G. PICK**[1];
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Abstract: Traumatic brain injury (TBI), is a brain dysfunction without present treatment, caused by a violent blow to the head. In models of various brain injuries, animals fed with ketogenic diet (KD) perform better on learning tasks than those fed standard diet (SD). The main goal was to examine whether KD has a neuroprotective effects on the cognitive deficits in the mTBI mouse model. Mice were fed ketogenic or standard diet starting immediately following the trauma. Cognitive and behavioral performance was assessed 7 and 30 days post injury using Elevated Plus Maze (EPM), Y-Maze and Novel Object Recognition (NOR) tasks. Tail blood was taken for determination of ketone bodies levels at 0, 3, 7 and 30 days post injury and SIRT1 levels in the cortex were assessed using western blot analysis 30 days post injury. The results of the Y-maze and NOR tasks showed that mTBI mice maintained on KD, showed better cognitive abilities than the mice fed SD. EPM analysis shows no difference between all groups, indicating that injury failed to cause any anxiety-like behavior. Relative to control + SD mice, mice received KD (with or without mTBI) demonstrated a prominent increase in ketone bodies at 3, 7 and 30

days after the KD was initiated. Mice maintained on SD; post injury demonstrated SIRT1 reduction when compared with control and KD groups. These results support accumulating evidence that KD may be an effective approach to increase brain resistance to damage, and suggest a potential new therapeutic strategy for treating mTBI.

Disclosures: M. Har Even: None. **V. Rubovitch:** None. **S. Schreiber:** None. **C.G. Pick:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.08/I7

Topic: C.10. Brain Injury and Trauma

Support: The Fundamental Research Funds for the Central Universities (No.2018SCUH0053)

Title: MiR-212-5p attenuates ferroptotic neuronal death after traumatic brain injury by targeting Ptgs2

Authors: *X. XIAO[1], L. ZHANG[1,2], S. CAO[1], Y. JIANG[1], H. YAN[3], W. LIANG[1], L. GAO[2]; [1]Dept. of Forensic Genetics, West China Sch. of Basic Med. Sci. & Forensic Med., [2]Lab. of Mol. and Translational Medicine, West China Second Univ. Hosp., [3]Dept. of Forensic Pathology, West China Sch. of Basic Med. Sci. & Forensic Med., Sichuan Univ., Chengdu, China

Abstract: Ferroptosis, a newly discovered form of iron-dependent regulated cell death, has been indicated to be involved in traumatic brain injury (TBI). MiR-212-5p has previously reported to be downregulated in the extracellular vesicles after TBI. Here, we aimed to investigate whether miR-212-5p is involved in the ferroptotic neuronal death in TBI mice. The mRNA and protein levels of ferroptosis-related molecules were examined using qRT-PCR and western blotting, and the levels of ferrous iron and malondialdehyde (MDA) were measured by corresponding detection kits at 6h, 12h, 24h, 48h and 72h following controlled cortical impact (CCI) in mice. Cell death was examined using the lactic dehydrogenase assay in HT-22 and Neuro-2a cell lines transfected with miR-212-5p mimic and inhibitor. Luciferase report assay was applied to determine the target gene of miR-212-5p. Finally, the learning and spatial memory were evaluated using morris water maze test after stereotactically injecting miR-212-5p into the right lateral ventricle of CCI mice. The mRNA levels of *Gpx4* and *Acsl4* were upregulated at 6h post injury. The mRNA levels of *Nox2* and *Sat1* were constantly upregulated from 6h to 72h and the mRNA levels of *Slc7a11* were upregulated from 12h to 72h post injury. The protein levels were also observed to be significantly upregulated, with Gpx4 at 6h, Nox2 from 6h to 72h, xCT from 12h to 72h, and Sat1 at 72h after CCI. Interestingly, ferrous iron and MDA were increased

whereas miR-212-5p was decreased in the CCI group compared to the sham group from 6h to 72h post injury. Overexpression of miR-212-5p would attenuate ferroptosis while downregulation of miR-212-5p would promote ferroptotic cell death by targeting Ptgs2. Administration of miR-212-5p in CCI mice significantly improved the learning and spatial memory. Collectively, these findings indicate that miR-212-5p may protect against ferroptotic neuronal death in CCI mice partially by targeting Ptgs2.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.09/I8

Topic: C.10. Brain Injury and Trauma

Support: The General Research Fund grant from the Research Grant Council of the Hong Kong Special Administrative Region Government (Ref. No.: 11100318)

Title: Low dose ionizing radiation promotes motor functional restoration in a mouse model of traumatic brain injury

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Abstract: Traumatic brain injury (TBI) is a form of mechanical insult to the brain leading to irreversible motor functional impairments in TBI patients. TBI remains as a leading cause of disability and morbidity in the globe. The injured neurons in the central nervous system (CNS) have limited regenerative capacity to regrow their damaged axons across the lesion for target reinnervation following injuries. The presence of extrinsic growth inhibitory molecules such as chondroitin sulfate proteoglycans (CSPGs) at the lesion further impede axon regeneration after injuries. Currently, there is no effective therapy aimed to improve functional restoration in TBI patients. In recent years, emerging evidence suggested that low dose of ionizing radiation (LDIR) exhibits a wide range of beneficial effects to irradiated individuals. For instance, single exposure to LDIR exerts neuroprotective effects in various neurological disorders including Parkinson's disease, retinitis pigmentosa, glaucoma and spinal cord injury. This prompted us to investigate the potential hormetic effects of LDIR on promoting CNS repair after TBI. We performed a stab wound injury in motor cortex of postnatal and adult C57BL/6 mice, respectively. The mice were then received a single whole-body exposure of LDIR immediately after injury. In both postnatal and adult mice, LDIR markedly accelerated wound closure with a

marked reduction in apoptotic neurons 7 days after cortical stab wound injury. More importantly, we observed a marked improvement in motor functions from irradiated mice as assessed by pole climbing test, grip strength test and beam walking test after injury. Further histological analysis revealed that LDIR markedly increased microglial density, associated with a marked reduction in CSPG deposition at the lesion 6 hours and 7 days after injury. We confirmed that the increased microglial density at the lesion was due to the promoted microglial migration towards the lesion, but not due to increase in microglial proliferation. Cytokine profiling and qPCR analysis on irradiated microglia suggested that LDIR promoted microglial M1-to-M2 switch, with increased expression of genes involved in neuroprotection, CSPG degradation and phagocytosis. Taken together, our study demonstrated for the first time that LDIR promoted CNS repair and functional restoration via immunomodulation of microglia after TBI, shedding new light in developing alternative therapeutic approaches for TBI patients to improve functional outcomes after injuries.

Disclosures: C.H.E. Ma: None. **N.P.B. Au:** None. **S.L. Chan:** None. **K.N. Yu:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.10/I9

Topic: C.10. Brain Injury and Trauma

Support: PAPIIT, DGAPA IN: 214017 (scholarship to S. Garcia-Rios)
PAPIIT, DGAPA IN: 223417

Title: Expression of brain cortex CB_1 and CB_2 cannabinoid receptors in rats with traumatic brain injury treated with repetitive low frequency transcranial magnetic stimulation

Authors: S. GARCIA-RIOS[1], S. VALADEZ-IBARRA[1], M. MARTINEZ-VARGAS[1], L. NAVARRO[2], *L. VERDUGO-DIAZ[1];
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Abstract: Transcranial Magnetic Stimulation (rTMS) is a technique which uses an electromagnetic field to induce changes in excitability of brain tissue. This property results useful as a treatment against Traumatic Brain Injury (TBI), a disease in which, among other things, deregulates the excitability of the brain, leading to neural damage. Against a TBI, the brain activates endogenously protective mechanisms, such as the activation of the cannabinoid system, which will regulate the excitability of neurons via their CB1 and CB2 receptors. In this study we evaluated the effects of low frequency (1 Hz) rTMS on the expression of brain cortex CB1 and CB2 receptors in Wistar rats with TBI. TBI was induced using a closed skull weight-

drop injury, with a metallic piston at 40 psi pression on the exposed and unprotected skull at the level of the motor cortex (coordinates $P = -2$ and $L = 1.4$). To apply rTMS we used an In-House Electronic System (EMAGPRO 12). This system was designed and developed by engineers at the Center of Research and Advanced Studies, IPN (Mexico City). 1 Hz rTMS was applied for 7 days 10 minutes daily with a figure-eight coil. Furthermore, we evaluated the expression of cannabinoid receptors CB1 and CB2 through Western Blot and RT-PCR analysis. Additionally, we performed a behavior scale using the Neurobehavioral Severity Scale (NSS-R), to assess the effects that TBI had upon the motor skills of the rats and see if low frequency rTMS had a positive effect on this trait. The level of expression of the cannabinoid receptors, as well as the results of the behavioral scale differ within all our experimental and control groups. We concluded that the rTMS modifies the excitability of the brain cortex, thus altering the expression of CB1 and CB2 receptors, leading to changes in the outcome of the TBI.

Disclosures: S. Garcia-Rios: None. **S. Valadez-Ibarra:** None. **M. Martinez-Vargas:** None. **L. Navarro:** None. **L. Verdugo-Diaz:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.11/I10

Topic: C.10. Brain Injury and Trauma

Support: PAPIIT, DGAPA IN: 214017 to L.V-D
PAPIIT, DGAPA IN: 223417 to L. N

Title: Effect of high frequency transcranial magnetic stimulation on the expression of brain cortex CB_1 and CB_2 cannabinoid receptors of rats with traumatic brain injury

Authors: S. VALADEZ-IBARRA[1], S. GARCÍA-RIOS[2], L. VERDUGO-DIAZ[3], M. MARTÍNEZ-VARGAS[2], *L. NAVARRO[4];
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Abstract: Traumatic Brain Injury (TBI) is defined as an alteration in brain function or other evidence of brain pathology, caused by an external force. Neuroprotective therapy aims to minimize the activation of toxic pathways and enhance the activity of endogenous neuroprotective mechanisms. Endocannabinoid system has been found as a mechanism of self-protection with neuroprotective properties, and repetitive Transcranial Magnetic Stimulation (rTMS) has been propose as a potential treatment for TBI. However, there are no studies that

prove if rTMS affects the endocannabinoid system after a TBI. Therefore, the objective of the current study was to determine the effect of high frequency rTMS on the expression of CB1 and CB2 cannabinoid receptors in rats with traumatic brain injury. We used adult male rats of Wistar strain, which were subjected to a TBI using a closed skull weight-drop injury, with a metallic piston at 40 psi pression, was induced on the exposed and unprotected skull at the level of the motor cortex (coordinates $P = -2$ and $L = 1.4$). Subsequently treated with 10 Hz rTMS for 7 days, 10 minutes daily. To apply it, we used a figure-eight coil with an In-House Electronic System (EMAGPRO 12), that was designed and developed by engineers at the Center of Research and Advanced Studies, IPN (Mexico City). The behavior was analyzed with the Revised Neurobehavioral Severity Scale (NSS-R). The food consumption was recorded before and after the trauma. The expression of cannabinoid receptors in the cerebral cortex was analyzed by western blot and RT-PCR. Finally, the results were statistically analyzed by using the Prism program. There was no significant difference in food consumption, but there was a tendency to reduce food consumption after trauma. Preliminary results suggest that rTMS change the expression of CB1 and CB2 cannabinoid receptors. The results of NSS-R scale show an improvement in rats treated with high frequency rTMS compared to untreated animals. These results suggest that high frequency rTMS may be a potential treatment for TBI.

Disclosures: S. Valadez-Ibarra: None. **S. García-Rios:** None. **L. Verdugo-Diaz:** None. **M. Martínez-Vargas:** None. **L. Navarro:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.12/I11

Topic: C.10. Brain Injury and Trauma

Support: NRF-2018R1A4A1020922
NRF-2017M3C7A1028937
NRF-2017R1D1A1A09081190
NRF-2016M3C7A1913844

Title: Effects of the transient receptor potential cation channel 5 inhibitor on hippocampal neuronal death after traumatic brain injury

Authors: *M. PARK, B. CHOI, A. KHO, S. LEE, D. HONG, J. JEONG, B. KANG, D. KANG, S. SUH;
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Abstract: Traumatic brain injury (TBI) occurs when an external force impacts the brain. Head injury encompasses a variety of injuries that may involve damage to other structures such as the

scalp and skull. Traumatic brain injury can cause physical, cognitive, social, and behavioral changes and even permanent disability or death. When traumatic brain injury occurs, vesicular zinc is excessively released into the synaptic cleft and is then translocated into post synaptic neurons through multiple receptors and channels, such as the AMPA receptor, transient receptor potential cation channels (TRPCs) and transient receptor potential melastatin (TRPM). After primary brain injury, translocated free zinc can accumulate in neurons and lead to secondary events such as oxidative stress, inflammation, edema, swelling and cognitive impairment. Transient receptor potential channel 5 (TRPC5) is one of the seven mammalian transient receptor potential cation channels (TRPCs) that regulate the influx of cations such as calcium and sodium. The predominant TRPC channels are the TRPC1,4, and 5 in the mammalian brain and they are expressed in the hippocampus and prefrontal cortex of the brain regions. Specifically, TRPC4 and TRPC5 are associated with the mechanism of mercury toxicity and neurological behavior. Under pathological conditions such as ischemia and traumatic brain injury, excessive zinc release and accumulation occurs in neurons. Excessive zinc leads to calcium influx via TRPC5, leading to neuronal cell death. Based on previous research, we hypothesized that TRPC5 would induce zinc as well as calcium entry. Therefore, we hypothesized that the suppression of TRPC5 would prevent neuronal cell death by reducing the influx zinc and calcium. To confirm our hypothesis, we used a TBI animal model and after the TBI, we immediately injected NU6027(1mg/kg, *i.p),*TRPC5 inhibitor, and then sacrificed animals 24 hours later. We conducted Fluoro-Jade B (FJB) staining in order to confirm degenerating neuronal death in the cornus ammonis 1 (CA1) and the dentate gyrus (DG) of the hippocampus. As a result, degenerating neuronal cell death was decreased in the NU6027-treated group compared to the vehicle-treated group after TBI. In conclusion, the present study suggests that the suppression of TRPC5 can open a new therapeutic window for reduction of the neuronal death that may occur after TBI. Key Words: traumatic brain injury, zinc, NU6027, transient receptor potential cation channel 5, neuronal death

Disclosures: **M. Park:** None. **B. Choi:** None. **A. Kho:** None. **S. Lee:** None. **D. Hong:** None. **J. Jeong:** None. **B. Kang:** None. **D. Kang:** None. **S. Suh:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

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Program #/Poster #: 480.13/I12

Topic: C.10. Brain Injury and Trauma

Support: by Intramural Program of NIAAA, NIH and the Department of Defense in the Center for Neuroscience and Regenerative Medicine

Title: N-docosahexaenoylethanolamine (synaptamide) GPR110-dependently reduced gliosis and improved spatial memory deficit induced by mild repetitive traumatic brain injury

Authors: *H. CHEN, A. DESAI, H.-Y. KIM;
NIAAA/NIH, Rockville, MD

Abstract: Long-lasting complications of repetitive mild traumatic brain injury (rmTBI) has been linked with chronic neurodegenerative disorders, especially the development of chronic traumatic encephalopathy (CTE). To date, there have no effective treatments for the complications of rmTBI in clinic. N-docosahexaenoylethanolamine (synaptamide) is an endogenous metabolite of docosahexaenoic acid (DHA) that is highly enriched in the brain. Synatamide was shown to potently promote neurogenesis, neuritogenesis and synaptogenesis in developing neurons, and ameliorate LPS-induced neuroinflammation. Recently, we have demonstrated that GPR110 is the target receptor for synaptamide mediating synaptamide's bioactivity. We have also established that repeated Closed-Head Impact Model of Engineered Rotational Acceleration (rCHIMERA), a mouse model of traumatic brain injury (TBI), produces long-lasting neuropathology and memory deficit. Using this injury model, we investigated in this study the effects of synaptamide on biochemical and functional outcome of TBI. Adult C57BL/6 male wild-type (WT) and GPR110 knock-out (GPR110 KO) mice were subjected to CHIMERA injury or sham treatment for three consecutive days at 24 h interval. Immediately after each impact, mice were injected with synaptamide or vehicle intraperitoneally. They were euthanized at different time-points from the last injury. Immunohistochemical and Western blot analyses were performed for GFAP and Iba-1 to assess astrocyte and microglial activation, respectively. Morris water maze was conducted for functional outcome. rCHIMERA injury caused spatial memory deficit and prolonged activation of microglia and astrocyte in multiple brain areas including optic tract, corpus callosum, cortex and hippocampus from both WT and KO mice. After injury, gpr110 was elevated in the WT mouse brain and synaptamide significantly improved the spatial memory and suppressed the activation of microglia and astrocyte. In contrast, the synaptamide treatment following rCHIMERA produced no improvement in GPR110 KO mice. Our data indicate that synaptamide exerts GPR110-dependent specific neuroprotective effects, suggesting translational potential of GPR110 activation in repetitive mild TBI.

Disclosures: H. Chen: None. **A. Desai:** None. **H. Kim:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.14/I13

Topic: C.10. Brain Injury and Trauma

Support: Merit Review Award # 1 I01 RX003123-01A1, from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D)

Title: A potential experimental therapy for TBI-induced disabilities in a rodent model

Authors: *P. K. BOSE[1,2,3], J. HOU[1,2], S. TSUDA[1,2], R. NELSON[1], D. PLANT[1], K. RICHARDSON[1], I. ANWAR[1], J. GODIN[1], R. MARTIN[1], A. SADEESHKUMAR[1], V. BAEZ[1], T. S. YOUN[1,3], R. J. BERGERON[4], F. J. THOMPSON[1,2,5];
[1]Brain Rehabil. Res. Ctr., North Florida/South Georgia Veterans Hlth. Syst., Gainesville, FL; [2]Physiological Sci., [3]Neurol., [4]Medicinal Chem., [5]Neurosci., Univ. of Florida, Gainesville, FL

Abstract: There is a need to increase our understanding of TBI-induced long-term disability mechanisms, and to test the safety and efficacy of therapeutic measures that target these mechanisms utilizing approaches that have excellent potential for rapid translation. Acceleration/deceleration closed head traumatic brain injury (CH-TBI) induces damage of micro-vessels which results in endothelial shear injury, blood brain barrier (BBB) dysfunction, and micro-bleeding. Microbleed-derived iron can provide an enduring inflammation, further breakdown of the BBB tight junctions, and cell death through multiple inflammatory pathways. Thus, removal of toxic iron is potentially an important therapeutic design for TBI treatment and rehabilitation. Thus, the current studies tested the influence of injury and compared the therapeutic impact of 2 iron chelators on hallmark disabilities in a rodent model of CH-TBI. Mild/moderate CH-TBI was produced using our previously reported protocol (450 g/1.25m). NaHBED (n=10) and Deferoxamine (DFO; n=5) treatments were initiated PO Day-0 and continued through PO Wk-2 (50 mg/kg/day for 2 wks, SQ). The control animals received equal volume of saline (SQ; n=7). The outcome measures for spasticity, balance, gait, anxiety and cognitive functions were compared in the saline control and 2 iron chelators treated groups. Our data to date revealed long-term disabilities in motor/vestibulomotor, anxiety and cognitive behaviors following CH-TBI, and significant reductions in these disabilities by NaHBED treatment. By comparison, the DFO treatment was less effective in reducing spasticity. This difference in treatment efficacy might be due to the comparatively lower iron clearing potency of DFO. Immunohistochemistry studies of TBI tissues showed patterns of a) iron deposition and disruption of BBB, b) increased expression of markers for inflammation in each neural region essential for the studied behaviors, and c) loss of regulatory noradrenergic and trophic supports. Tissues from the NaHBED-treated animals exhibited robust normalization of each of these markers. Collectively, our studies demonstrate that: 1) iron deposited via TBI-induced BBB disruption accelerates neuroinflammation and neuronal cell death, and 2) these can be attenuated by an iron chelator treatment. Taken together, iron chelator treatment offers the potential for a mechanism-based therapy that addresses a significant contributor to long-term TBI disabilities, and contributes to trophic support for neuronal and vascular healing, and neuroplasticity for adaptive compensation. NaHBED revealed superior outcomes when compared with treatment using DFO.

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Sadeeshkumar: None. **V. Baez:** None. **R.J. Bergeron:** None. **F.J. Thompson:** None. **T.S. Youn:** None.

Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.15/I14

Topic: C.10. Brain Injury and Trauma

Support: Merit Review Award # 1 I01 RX003123-01A1, from the United States (U.S.) Department of Veterans Affairs Rehabilitation Research and Development Service (RR&D)

Title: Induction of the NF-kB signaling pathway, proinflammatory cytokines, and pyroptosis in the sensorimotor cortex, central nucleus of amygdala and locus coeruleus following TBI in rats

Authors: *S. TSUDA[1,2], J. HOU[1,2], R. NELSON[1], A. SADEESHKUMAR[1], V. BAEZ[1], F. J. THOMPSON[1,2,3], P. BOSE[1,2,4];
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Abstract: Over 10 million people in the world have annually been suffering from traumatic brain injury (TBI) morbidities. Most of these injuries are classified into mild/moderate closed-head TBIs (cTBIs) which reported to have risk factors for inflammation-induced further progressive diseases. Acceleration-deceleration cTBI can cause micro-vessel shear injury, blood brain barrier (BBB) dysfunction, and bleeding. Iron deposited by diffuse micro-bleeds fuels inflammation through reactive oxygen species, and multiple inflammatory pathways, which may induce progressive disabilities. Our laboratory has shown that the BBB was compromised in various brain regions following cTBI and activated the TLR4/NF-kB signaling pathway in the hippocampus. Importantly, these detrimental biological events were attenuated following an iron chelator (NaHBED) therapy, indicating that removal of toxic iron deposited in the brain is an effective anti-inflammatory therapeutic option following cTBI. However, in other brain regions, NF-kB-mediated inflammatory status has not well been studied following cTBI. Therefore, the purpose of this study was to investigate the cTBI-induced NF-kB signaling pathway, cytokine induction, and inflammation-induced programmed cell death (i.e., pyroptosis) in the sensorimotor cortex (SMCx), the central nucleus of amygdala (CeA) and the locus coeruleus (LC). Following mild/moderate cTBIs (450g/1.25m) in rats, the coronal brain sections of intact and cTBI animals were immnofluorescently labelled with antibodies against NeuN, toll-like receptor 4 (TLR4), and p-NF-κB (p65 phosphorylated at serine 536), proIL-1β, TNFα, caspase-1, cleaved IL-1β, gasdermin D, and dopamine beta-hydroxylase. Our data to date indicate that cTBI activated the NF-κB via TLR4, induced proinflammatory cytokines (proIL-1β, TNFα), and

triggered pyroptosis in the neuronal cells of the SMCx and LC. In contrast, NF-κB was activated only in non-neuronal cells without involving TLR-4 in the CeA. Nonetheless, expression of TNFα and pyroptosis was highly induced in neuronal cells of the CeA. These results together with our previous work suggest that iron deposited via cTBI-induced BBB disruption might partly be responsible for increased induction of NF-κB signaling, proinflammatory cytokines, and pyroptosis in the SMCx and CeA. Since the iron chelator, NaHBED, significantly attenuated cTBI-induced LC cell loss, iron chelator treatment could be a potential therapeutic option to improve TBI-induced progressive disabilities. The current study provides new information of cTBI-induced CNS pathology, which might contribute to the development of a novel therapy.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 480.16/I15

Topic: C.10. Brain Injury and Trauma

Support: Athletic and Human Performance Research Center, Marquette University

Title: The effects of intentional performance suppression on implicit sensorimotor adaptation

Authors: *D. LANTAGNE[1], L. A. MROTEK[1], J. B. HOELZLE[2], D. G. THOMAS[4], C. S. SMITH[3], A. J. GROVE[3], R. A. SCHEIDT[1,5,6];
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Abstract: Athletes in contact sports are at high risk for concussive events and often undergo cognitive baseline testing to aid in concussion diagnosis and recovery tracking. About 30% of athletes are suspected of intentionally suppressing baseline test scores. We developed a sensorimotor task that is sensitive to concussion and its recovery: participants reached repeatedly toward a spatial target while opposed by spring-like loads that changed unpredictably from trial to trial. We quantified the extent to which sensorimotor memories contributed to motor adaptation. The present study examines if our technique is resistant to intentional performance suppression. Eight subjects performed Cogstate computerized cognition testing and our reaching task. Subjects grasp the handle of a 2D horizontal planar robot and perform 190 ballistic out-and-back movements to a remembered target. During the reach, the robot applies a pseudorandom spring-like load that changes between trials. An ARX time series model was fit to the sequences

of reach errors and spring stiffness values to describe how implicit memories of reach performance contribute to sensorimotor adaptation. Between trials, subjects moved the handle to self-assess the accuracy of their prior reach. Subjects participated in two conditions. In one, they performed their best and in the other they attempted to intentionally suppress performance by simulating symptoms associated with concussion. We hypothesized that suppression will result in lower Cogstate scores as well as kinematic deficits in the robotic test, but will not show differences in how implicit memories contribute to sensorimotor adaptation. When suppressing the Cogstate tests, subjects scored below the normative range of healthy individuals. When suppressing the robot task, subjects took longer to reach the target, moved slower than normal, and performed with greater variability. Self-assessments during suppression had greater variability and took longer. Despite that, the time series model was resistant to the effects of suppression. The variance accounted for by the model was not different between conditions. Further, the model revealed no differences in how sensorimotor memories contribute to the rejection of errors caused by environmental uncertainty. These results provide preliminary evidence that the contributions of sensorimotor memories to motor adaptation cannot be intentionally suppressed, and that a robotic assessment of concussion severity based on sensorimotor adaptation will be resistant to intentional performance suppression.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

Location: Hall A

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Program #/Poster #: 480.17/I16

Topic: C.10. Brain Injury and Trauma

Support: NSERC Grant

Title: Growth differentiation factor 11 promotes survival of retinal ganglion cells *in vitro* and *in vivo*

Authors: *H. YOO, U. SHANMUGALINGAM, D. CHAN, M. LUI, P. SMITH;
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Abstract: The visual system is a well-established model system to study axon regeneration and cell survival *in vitro* and *in vivo*. The use of this model has resulted in the identification of a variety of factors that improve cell survival and axonal growth after axon injury. Growth differentiation factor 11 (GDF11), a transforming growth factor-β (TGF-β) family member, was previously identified as a rejuvenation factor that promoted neurogenesis in aging mice. Previous work has revealed that *gdf11* mRNA is expressed in the developing retina, and that GDF11

protein can signal *Xenopus* retinal ganglion cell (RGC) growth *in vitro*. Previous work has revealed a striking decline in intrinsic RGC growth potential with age. The mechanisms mediating this dramatic loss of axonal growth ability has fueled significant interest in defining the factors that could contribute to this limitation in growth ability. The potential regenerative effect of GDF11 on mammalian RGCs remain unclear. Experiments were designed to determine whether GDF11 treatment promotes RGC survival and axonal growth using *in vitro* RGC culture and *in vivo* optic nerve crush models. Our data revealed that GDF11 administration was sufficient in protecting RGCs both *in vitro* and *in vivo*, but did not promote axonal growth. Our data also suggest that GDF11 promotes its neuroprotective effects *via* activation of phospho-Smad2/3 *in vitro*.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

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Topic: C.10. Brain Injury and Trauma

Support: NIH P30-GM122733

Title: Regulating neuronal growth with structurally-defined glycans

Authors: *G. HARTMAN, H. LUI, A. A. VASCONCELOS, V. POMIN, J. SHARP, N. M. ASHPOLE;
Univ. of Mississippi, Oxford, MS

Abstract: Chondroitin sulfate proteoglycans (CSPGs) and keratan sulfate proteoglycans (KSPGs) play an important role in neural development. Aggrecan, a CSPG, operates in the neural extracellular matrix where it negatively regulates neurite outgrowth to prevent aberrant process formation. Unfortunately, this aggrecan or CSPG-rich/KSPG-rich barrier can also prevent neuronal regeneration, which contributes to the inability to repair brain and spinal cord injuries. Removal of CSPGs and KSPGs has been shown to increase neurite outgrowth. We extend these findings by testing the ability of structurally-defined glycans to outcompete aggrecan and allow neurite outgrowth. Our overall goal is to determine if there is a particular glycan structure which can overcome inhibitory CSPGs and KSPGs without inhibiting neurite outgrowth themselves. We utilized primary cultures of rat neurons and applied polydisperse structurally related mixtures of CSPGs, KSPGs and newly-isolated, novel glycans in the absence and presence of aggrecan. Several of these glycans successfully removed the aggrecan-induced blockade while not inhibiting neurite outgrowth on their own. We are currently investigating the

efficacy of these compounds in concentration-response curves and are testing additional glycans with different molecular weights and varying sulfation patterns to determine the structural requirements for the glycans as modulators of neurite outgrowth. By investigating the impacts of these glycans, we will increase the understanding of proteoglycan regulation of neural structure and function, and potentially identify compounds which could be used to treat spinal cord injuries.

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Poster

480. Traumatic Brain Injury: Mechanisms and Therapeutic Strategies

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Topic: C.10. Brain Injury and Trauma

Support: National Institute of Health Research Professorship (NIHR-RP-011-048) awarded to David Sharp. and supported by the NIHR CRF and BRC at Imperial College Healthcare NHS Trust

Title: Dynamic causal modelling of methylphenidate effects in traumatic brain injury

Authors: *M. BALAET;
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Abstract: Executive dysfunction (ED) after traumatic brain injury (TBI) is a major concern, since it impacts quality of life and independence. Corticostriatal networks are known to be impaired in disorders characterised by ED, and recent evidence suggests their disruption also underlies these symptoms in patients with head trauma. In particular, the structural and functional connectivity between the caudate and a distributed set of cortical regions appears to correlate with ED (De Simoni et al., 2017). Analysis was performed on multimodal DTI-fMRI data from 42 TBI patients and 21 age-matched controls. The results illustrate reduced integrity of the white matter tracts and reduced connectivity in these regions is associated with ED. The same cohort of patients underwent a placebo-controlled methylphenidate trial.
The aim was to use resting state fMRI data to assess the impact of TBI and that of methylphenidate on the functional connectivity between the caudate and the regions where methylphenidate produces an effect. We used a generative modelling technique called spectral dynamic causal modelling. We constructed fully connected four-node models comprising of the caudate self-connection, network to caudate connection, caudate to network connection and network self-connection. After testing the stability of the models, we contrasted them across groups and drug conditions. Correlations between the effect of the drug on the functional

connectivity and Stroop executive function neuropsychological measures were then performed. All directed connectivity patterns were reproducible across individuals and across baseline, drug and placebo sessions, different significantly across patient and control groups. There were reliable effects of drug, whereby the patient-control differences in functional connectivity were normalised. There was a significant effect of TBI on the right caudate and methylphenidate effect network four-node models. The connection between the methylphenidate effects network to the right anterior caudate which was impaired by TBI was normalised by methylphenidate. Similarly, the connection between the right posterior caudate to the methylphenidate effects network which was impaired in TBI was normalised by methylphenidate. There was also a significant effect of the drug on the left anterior caudate and methylphenidate effect network four-node model. There was no significant correlation between the drug normalisation effect and executive function measures.
These results pave the way towards understanding effective connectivity relating to ED in TBI. They also enable a better understanding of the mechanism of methylphenidate effects.

Disclosures: M. Balaet: None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.01/I19

Topic: C.11. Spinal Cord Injury and Plasticity

Support: DOH01-ISSCI6-2016-00018, NYSCIRB (OB)
ES_BI-2017, Christopher and Dana Reeve Foundation (SH)

Title: Lumbosacral spinal cord epidural stimulation reduces systemic inflammation in an individual with neurologically complete chronic SCI

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Abstract: In individuals with severe spinal cord injury (SCI), the autonomic nervous system (ANS) is affected leading to cardiovascular deficits and other impairments, which may result in hypotension, autonomic dysreflexia, and increased risk of stroke. Persons with SCI rostral to T5, where sympathetic nervous system fibers exit the spinal cord and innervate the immune system, also have clinically significant systemic inflammation and increased infection risk. We recently

identified profoundly elevated systemic inflammatory gene expression in persons with SCI rostral to T5 (Herman et al J Neurotrauma 2018). Based on our recent finding that lumbosacral spinal cord epidural stimulation (scES), using targeted configurations that promote cardiovascular stability (CV-scES), can safely and effectively normalize blood pressure in persons with chronic SCI (Harkema et al 2018 JAMA Neurol, Harkema et al 2018 Front Hum Neurosci), we hypothesized that this intervention would improve the immunological profile for inflammation. We investigated if daily exposure to CV-scES, that successfully restored blood pressure stability, also altered whole blood gene expression in a person (female, age 27) with chronic clinically motor complete cervical SCI. Blood was collected before and after 8 months of 6-hour daily CV-scES training. RNA was isolated from blood, mRNASeq libraries prepared (Illumina TruSeq Stranded Total RNA with RiboZero Globin), and 100bp paired end reads were collected on the Illumina HiSeq 2500 platform. With Partek Flow software, trimmed reads were aligned using STAR to the *hg38*genome assembly. There were 1040 up- and 590 down-regulated genes that were differentially expressed after CV-scES (FDR=0.05). Functional analysis of differentially expressed genes was performed using Enrichr (Chen et al 2013). The Panther, Reactome and Biocarta databases indicated that expression of several inflammatory pathways were downregulated, including Toll-like receptor signaling, cytokine and chemokine pathways. Conversely, Biocarta and Reactome databases indicated that the IL-10 anti-inflammatory pathway was upregulated after CV-scES. To our knowledge, this is the first report of data consistent with the hypothesis that scES may improve the immunological functional state in persons with chronic SCI.

Disclosures: O. Bloom: None. **A.V. Ovechkin:** None. **C.A. Angeli:** None. **A. Arcese:** None. **S.J. Harkema:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.02/I20

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 1R01EB007615, National Institutes of Health
ES1-2011, Christopher and Dana Reeve Foundation
2011PG-MED011, Leona M. & Harry B. Helmsley Charitable Trust
ES2-CHN-2013, Craig H. Neilsen Foundation, Christopher and Dana Reeve Foundation
2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust
ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Human spinal circuitry generates intentional individual joint flexion after clinically diagnosed motor complete spinal cord injury with subthreshold lumbosacral epidural stimulation

Authors: *C. A. ANGELI[1,2], E. REJC[2], C. FERREIRA[2], S. J. HARKEMA[2,1];
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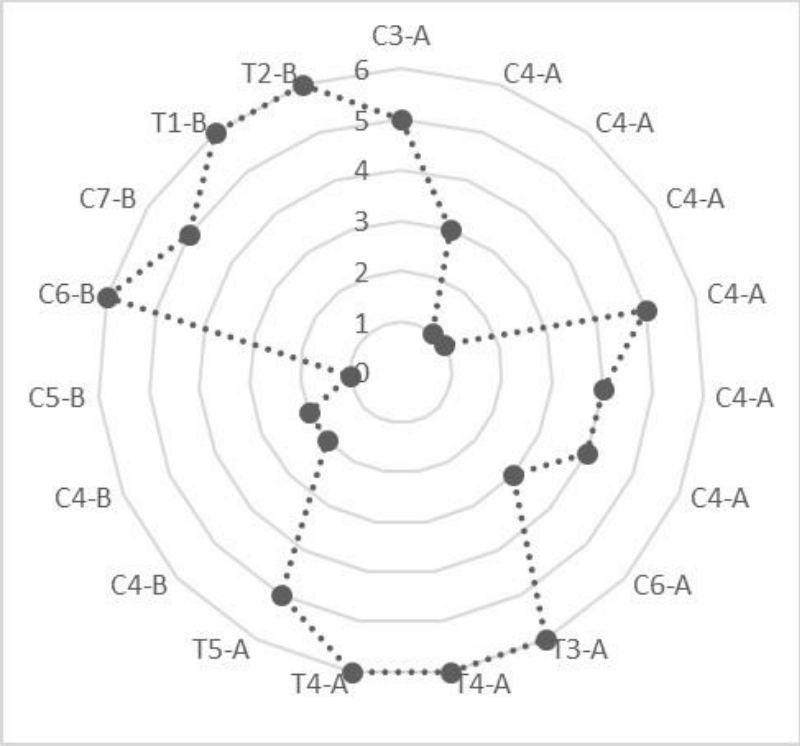
Abstract: Recovery of voluntary motor function several years after clinical diagnosis of motor complete spinal cord injury (SCI) is rare. Subthreshold network targeted lumbosacral epidural stimulation (scES) restored voluntary movement in 5 individuals with motor complete SCI (Angeli2014, Grahn2017). Suprathreshold spatiotemporal targeted scES elicited movement in motor incomplete SCI in muscles scored 0 (AIS scale) (Wagner2018). The aim of this study is to understand mechanisms of suprathreshold vs. subthreshold scES in generating joint flexion in individuals with motor complete SCI. Individuals with motor complete SCI (n=19) were implanted at L1-S1 SC level with an electrode and neurostimulator. These individuals (age: 29.5 ± 8.7 yrs; time post injury: 4.8 ± 2.7 yrs) were unable to move their legs voluntarily, stand or step independently. Neurophysiological mapping consisted of amplitude and frequency responses at 2Hz scES using adjacent bipolar electrode combinations providing threshold and activation patterns for lower extremity muscles. Next, voluntary movement mapping continued while asking individuals to attempt flexion movements of the first toe, ankle and hip. Further changes in parameters were dependent on observed EMG modulation and joint movements. We performed torque and EMG assessments in 6/19 cases and supine movement in 19/19. All individuals were able to modulate EMG activity in the presence of subthreshold scES and able to move at least one joint. Although suprathreshold scES could drive movement in all participants, all optimized scES were subthreshold to allow initiation and control of the movement. Six of 19 were able to move all six joints. Figure 1 shows the number of joints individuals were able to voluntarily move with optimized scES. Ability to move was not dependent on age, time since injury or neurological level. These results provide evidence the subthreshold scES modulates network excitability of the injured spinal cord to allow for the integration of afferent and supraspinal descending input to generate movement below the injury after motor complete SCI.



Disclosures: **C.A. Angeli:** None. **E. Rejc:** None. **C. Ferreira:** None. **S.J. Harkema:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.03/I21

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Christopher and Dana Reeve Foundation
ES2-CHN-2013, Craig H. Neilsen Foundation
2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust
ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Effects of epidural stimulation on splanchnic blood flow during tilt induced hypotension in an individual with chronic spinal cord injury

Authors: *J. D. GUEST[1], A. V. OVECHKIN[2], B. LEGG DITTERLINE[3], J. FISHER[4], S. WADE[4], J. M. WECHT[5], S. J. HARKEMA[6];
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Consequences of Spinal Cord Injury, Icahn Sch. of Medicine, Mount Sinai, New York, NY; [6]Dept Neurol Surgery, Univ. Louisville, Frazier Rehab Inst, KSCIRC, Louisville, KY

Abstract: Introduction. Ultrasonography is a dynamic imaging tool to examine blood flow provided technical issues are controlled. In persons with chronic spinal cord injury (SCI), lumbosacral spinal cord epidural stimulation targeted to increase systolic blood pressure (CV-scES) has demonstrated beneficial changes in blood pressure regulation during orthostatic stress. The mechanisms responsible for these CV-scES-triggered blood pressure and flow changes are unknown, however sympathetic nervous system activation may play a role. Sympathetic activation could be associated with increased vascular resistance and a shift in blood volume from capacitance vessels into the active circulation, thereby increasing venous return and cardiac output. It is known that a substantial fraction of total blood volume is within the splanchnic vascular bed, thus, we hypothesized that celiac artery flow velocity would decrease in tilt and increase during active CV-scES Methods. To quantify such effects, dynamic changes in blood vessel area and pulsatility must be imaged. These measurements must be feasible under conditions that are clinically relevant, such as induced postural hypotension on a tilt table. To examine these issues, we focused on the celiac artery in an individual with C5, AIS B SCI (7.5 years post-injury) with known postural hypotension who had an epidural stimulator implanted at L1-S1 spinal cord. The pulsatile waveform (studied with a Philips Epiq 7G and C5-1 curved array transducer) provides information related to resistance in the vessels. Results. While supine, the celiac trunk varied from 5.9-8.6 mm diameter across the cardiac cycle (BP=106/67 mm Hg, 45 BPM). Peak systolic velocity was 300 mm/s with a resistivity index (RI) of 0.81. When the participant was tilted to approximately 50 degrees, peak velocity fell to 105 mm/s and vessel caliber ranged from was 5.0-7.4 mm; automated RI did not change but the diastolic wave form was unstable (58/35 mm Hg, 73 BPM. With active CV-scES of .8-.9V during tilt, RI decreased to 0.73, peak velocity increased to 145 mm/s, and flow during diastole was both greater and stable (BP 126/82 mm Hg, 60 BPM). Conclusion. These observations demonstrate active CV-scES changes celiac artery blood flow during postural hypotension.

Disclosures: J.D. Guest: A. Employment/Salary (full or part-time):; University of Miami. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aceso Therapeutics. F. Consulting Fees (e.g., advisory boards); Abbvie. **A.V. Ovechkin:** A. Employment/Salary (full or part-time):; University of Louisville. **B. Legg Ditterline:** A. Employment/Salary (full or part-time):; University of Louisville. **J. Fisher:** A. Employment/Salary (full or part-time):; University of Louisville. **S. Wade:** A. Employment/Salary (full or part-time):; University of Louisville. **J.M. Wecht:** A. Employment/Salary (full or part-time):; Bronx VA Medical center. **S.J. Harkema:** A. Employment/Salary (full or part-time):; University of Louisville.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.04/I22

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust ES_BI-2017 Christopher and Dana Reeve Foundation

Title: Human spinal networks identified in modulating cardiovascular function independent from other functions

Authors: *G. F. FORREST[1], S. KIRSHBLUM[2], W. JILL[3], B. LEGG DITTERLINE, PHD P[4], C. A. ANGELI[6], E. REJC[5], S. J. HARKEMA[7];
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Abstract: **Introduction:** Lumbosacral spinal cord epidural stimulation (scES) can locate and activate autonomic and motor neuron pools by systematically changing individual electrode polarity, frequency, amplitude, and pulse burst. Muscle activation and blood pressure data obtained from neurophysiological spinal mapping provides targeted configurations to elicit voluntary motor behaviors (Motor-scES) or physiological responses (CV-scES) to elicit cardiovascular stability. This study evaluated the specificity of the spinal neural networks for modulating cardiovascular function by comparing the efficiency of Motor-scES daily training to CV-scES daily training for targeting chronic orthostatic hypotension and modulating cardiovascular function **Methods:** Seven individuals with chronic motor complete cervical SCI *having cardiovascular dysregulation* received CV-scES (n=4) or Motor-scES (n=3) spatial temporal neurophysiological mapping. CV-scES mapping for systolic blood pressure stability in the range of 110 -120 mmHg did not invoke any motor activation in the lower extremity or trunk. Before and after 80 sessions of CV-scES or Motor-scES training, blood pressure, heart rate (HR) without scES were recorded during orthostatic stress induced by sit-up test. Individuals lay supine for at least 15 minutes, passively moved to a seated position; finger plethysmography and ECG recorded beat-to-beat blood pressure and HR. **Results:** Before CV-scES training, mean sitting blood pressure (90±6/54±4 mmHg) significantly decreased compared to supine blood pressure (103±3/60±3 mmHg). Mean sitting HR (72±3 bpm) significantly increased compared to supine HR (51±3 bpm). After CV-scES training, mean sitting (107±6/63±4 mmHg, 66±5 bpm) outcomes compared to supine (103±3/60±3 mmHg, and 63±3 bpm) were not significantly different. Orthostatic blood pressure stability was maintained regardless orthostatic stress. Before

Motor-scES training, mean sitting blood pressure (100±13/54± 8) decreased compared to supine blood pressure (115±12/59±8 mmHg) and mean sitting HR (65±8 bpm) significantly increased compared to supine HR (53±5 bpm). After Motor-scES training mean sitting blood pressure (84±6/47±1 mmHg) compared to supine (110±19/59±8 mmHg) significantly decreased; mean sitting HR (55±7,66±6 bpm) significantly increased. **Conclusion:** Specificity of spinal cord networks elicit independent and unique temporal spatial maps for autonomic regulation. Motor-scES mapping is specific to motor pools with negative or no effect on cardiovascular function. This research has implications for intersystem networks for restoration of health and function after SCI.

Disclosures: G.F. Forrest: None. **S. Kirshblum:** None. **C.A. Angeli:** None. **S.J. Harkema:** None. **E. Rejc:** None. **B. Legg Ditterline, PhD P:** None. **W. Jill:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.05/I23

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH SPARC OT2OD024898

Title: Epidural stimulation of the lumbosacral cord to promote storage and stimulate voiding in urethane-anesthetized transected female rats

Authors: *C. HUBSCHER[1], R. HOEY[1], D. MEDINA AGUINAGA[1], F. KHALIFA[2], S. ZDUNOWSKI[1], A. EL-BAZ[2], S. HARKEMA[1];
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Abstract: Daily bladder management for conditions such as spinal cord injury (SCI) most frequently includes a combination of catheterization (either self-intermittent or suprapubic) and pharmacological approaches, which targets maintenance but does not promote recovery of function. We have exciting data from multiple individuals receiving spinal cord epidural stimulation (scES) that is optimized for stepping and standing, in combination with task-specific training, that shows improvements in lower urinary tract function. The overall objective of our current functional mapping pre-clinical animal studies is to identify scES configurations (electrode location, amplitude and frequency) at lumbosacral spinal levels that can promote and/or provide optimal neural control of urine storage (adequate bladder capacity at safe pressures without incontinence) and sufficient controlled emptying (high voiding efficiency at safe leak point pressures) after SCI. Initial mapping was done in acute anesthetized terminal preparations during cystometry (bladder filling) using a modified electrode array (Medtronic

Specify 5-6-5 epidural device) that is being used by our group in parallel human scES studies. The current data compares the response to scES in transected female rats 6 weeks post-injury at L3 (region with circuits related to external urethral sphincter [EUS] control) and L6 (level of bladder circuits) spinal segments. Results: 1) L3 stimulation through activation of EUS reduced void volume but did not prevent bladder contractions. 2) L3 stimulation showed a frequency and intensity dependent pattern of results, indicating the rate of stimulation is important for EUS function. 3) L6 stimulation immediately triggered contraction of the bladder and voiding. 4) L6 stimulation is intensity but not frequency dependent. Taken together these results suggest that the circuitry is dissociable and amenable to stimulation that seeks to promote either storage or voiding. Furthermore, our innovative approach and novel application of this Medtronic Specify 5-6-5 epidural device will generate functional maps that will lay the groundwork for expedient translation of this promising technology to individuals with SCI as well as provide a powerful tool for elucidating underlying circuits present in the lumbosacral cord that are involved in urogenital function.

Disclosures: C. Hubscher: None. **R. Hoey:** None. **D. Medina Aguinaga:** None. **F. Khalifa:** None. **S. Zdunowski:** None. **A. El-Baz:** None. **S. Harkema:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.06/I24

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH SPARC OT2OD024898

Title: Response of distal colon and rectum to epidural stimulation of the lumbosacral cord in Wistar rats under urethane anesthesia

Authors: *R. F. HOEY[1], D. MEDINA AGUINAGA[1], F. KHALIFA[3], S. ZDUNOWSKI[2], A. EL-BAZ[3], S. HARKEMA[2], C. HUBSCHER[1];
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Abstract: Numerous complications arise after spinal cord injury (SCI) including bowel dysfunction, with up to 95% of individuals requiring at least one method of initiating a bowel movement (e.g. laxatives, digital stimulation). Bowel dysfunction after SCI is most often due to reduced gastric and colonic motility (constipation, fecal impaction, difficulty with evacuation) with the additional complication of incontinence due to lack of rectal/anal sensation and control. Our lab has been investigating the effect of spinal cord epidural stimulation (scES) on bowel function in an animal model utilizing spinal cord transection (T9) and spinally intact male and

female Wistar rats (contusion injuries planned) in an acute anesthesia (urethane, IV) terminal preparation. Using a modified Medtronic 5-6-5 electrode, the L5-S1 segments of the cord were targeted and numerous stimulus combinations (frequency, Hz; intensity, µA) were applied to determine the effect on distal colon, rectal, and anal sphincter function. To measure bowel function, pressure probes (Millar SPR-524, 3.5F tip) were positioned at depths of 2 cm (rectum) and 10 cm (distal colon) from the anal verge. Anal sphincter function was measured by implanting fine-wire electrodes bilaterally into the external anal sphincter. Baseline data collected prior to scES is compared to those data collected during stimulation periods to assess any effect on bowel contraction activity in these structures. Dependent measures for pressure recordings include: the presence of contractile waves, frequency of contractions, amplitude of contraction, and whether the contractions are stimulated or inhibited by the epidural stimulation. The data collected to date indicate 1) scES stimulation of the L5-S1 cord inhibits the contractile activity of both the distal colon and rectum, 2) this inhibition is intensity but not frequency-dependent, and 3) the inhibition is not sex dependent. Additionally, because data regarding bowel and bladder function can be collected concurrently, any interaction or dynamic interplay in these systems can be investigated. Furthermore, the ability to control multiple system dysfunctions with a single intervention is an exciting possibility for the treatment of human SCI using scES.

Disclosures: R.F. Hoey: None. **D. Medina Aguinaga:** None. **F. Khalifa:** None. **S. Zdunowski:** None. **A. El-Baz:** None. **S. Harkema:** None. **C. Hubscher:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.07/I25

Topic: C.11. Spinal Cord Injury and Plasticity

Support: Leona M. and Harry B. Helmsley Charitable Trust
Craig H. Neilsen Foundation
Department of Defense USAMRAA/CDMRP/DoD W81XWH-14-2-0190

Title: Effects of wide pulse width neuromuscular electrical stimulation and afferent feedback on activation pattern modulation in individuals with severe spinal cord injury

Authors: *D. J. ARPIN[1], B. UGILIWENEZA[1], G. F. FORREST[2], S. J. HARKEMA[3], E. REJC[1];
[1]Univ. of Louisville, Louisville, KY; [2]Kessler Fndn., West Orange, NJ; [3]Dept Neurol Surgery, Univ. Louisville, Frazier Rehab Inst, KSCIRC, Louisville, KY

Abstract: Severe spinal cord injury (SCI) results in the inability to stand and step, primarily because of the loss of tonic supraspinal drive to the spinal circuits controlling posture and locomotion, compromising the level of excitability of this circuitry. In the last decade, spinal cord stimulation has been applied to enhance the excitability of the spinal circuitry to promote motor function recovery after sever SCI. Interestingly, wider pulse width neuromuscular electrical stimulation (NMES) has been proposed to favoring central (spinal) activation mechanisms. Thus, specific NMES parameters may modulate the excitability of the spinal circuitry, which could affect training-induced neural plasticity and consequent motor function recovery in individuals with sever SCI. Therefore, this study explored the effect of NMES pulse width on central activation in 10 individuals (female = 2, male = 8; age = 33.9 + 9.5 years) with motor complete SCI. To this end, NMES was delivered to the knee extensors and ankle plantarflexors starting with an amplitude of 5 mA, and increasing by 5 mA for every subsequent stimulation until either the participant requested to stop the stimulation or the maximum stimulation amplitude (140 mA) was reached. This stimulation protocol was repeated with two pulse widths (500 and 1000 us), which were randomized across participants and muscle groups. To investigate the effects on central activation, electromyographic (EMG) activity was concurrently recorded from the vastus lateralis during knee extension stimulation, and from the gastrocnemius medialis during plantarflexion stimulation. Our results show that the higher pulse width (1000 us) demonstrated a greater effect on central activation as quantified by more frequent occurrences of post-NMES EMG activity ($p = 0.002$) and a 37% higher EMG amplitude ($p = 0.003$) in contractions generating similar torque output. We also found inter-individual differences in how NMES amplitude and torque output affect central activation. These findings suggest that pulse width should be carefully selected, together with the other NMES parameters, to optimize the neuromuscular activation depending on the rehabilitative goal (i.e. maximizing torque generation or central activation). Furthermore, preliminary data suggests that wide-pulse NMES may be used to enhance central activation for a short time period, during which afferent information alone (i.e., movement of the knee joint) could enhance muscle activation. Further studies should examine whether this brief period can provide a time-window during which greater training-induced neural plasticity can be promoted.

Disclosures: D.J. Arpin: None. **B. Ugiliweneza:** None. **G.F. Forrest:** None. **S.J. Harkema:** None. **E. Rejc:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.08/I26

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 1R01EB007615, National Institutes of Health

ES1-2011, Christopher and Dana Reeve Foundation
2011PG-MED011, Leona M. & Harry B. Helmsley Charitable Trust

Title: The human spinal cord can concurrently learn standing and stepping after chronic motor complete spinal cord injury

Authors: *E. REJC[1], C. A. ANGELI[2], S. HARKEMA[1];
[1]Univ. of Louisville, Louisville, KY; [2]Frazier Rehab Inst., Louisville, KY

Abstract: Increasing evidence suggests that spinal cord epidural stimulation (scES) and activity-based training can promote significant motor function recovery after chronic, motor complete spinal cord injury (SCI). Previous studies in complete animal models showed that the motor tasks that are repetitively practiced affect the characteristics of training-induced neural plasticity, leading to task-specific adaptations and also affecting the spinal cord ability to learn novel motor tasks. The aim of this study is to further explore the learning potential of the human spinal cord following motor complete SCI, understanding *i*) whether standing and stepping, two motor patterns that differ considerably in neural activation, can be concurrently learnt; and *ii*) which training characteristics are important to promote the recovery of standing and stepping. Eight individuals with chronic, motor complete SCI were implanted with a scES unit. Four individuals performed approximately 80 sessions of stand training (5 days/week; 1 hour per session) followed by ~80 sessions of step training (Cohort 1). Four other individuals (Cohort 2) alternated standing and stepping practice every session (stand-step training), achieving the same training volume as Cohort 1 (~160 sessions). Cohort 2 also gradually increased training frequency (i.e. 2 sessions/day), and was encouraged to volitionally contribute to the motor pattern generation. Training was always performed with individual- and task-specific scES. Stand training improved standing ability in all individuals enrolled in Cohort 1, with two of them achieving independent standing with self-assistance for balance. The subsequent block of step training impaired standing ability in three of these four participants. Also, Cohort 1 was unable to take independent steps on a treadmill at any time point. Cohort 2 showed progressive improvement in standing ability (less external assistance and less stable upper limb support) throughout stand-step training, and all individuals achieved independent standing holding the hands of a trainer to assist balance. Also, independence of different components of the step cycle progressed throughout stand-step training in Cohort 2, and three participants achieved independent steps on a treadmill; the intent to step was critical to generate this motor output. These findings suggest that, after motor complete SCI, the human spinal cord can concurrently learn standing and stepping while appropriate scES parameters are applied, and that varying the trained motor task as well as volitionally contributing to the motor pattern generation are key training features.

Disclosures: E. Rejc: None. **C.A. Angeli:** None. **S. Harkema:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.09/I27

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2011PG-MED011, Leona M. & Harry B. Helmsley Charitable Trust

Title: Neurophysiological markers and machine learning to support the selection of epidural stimulation parameters for standing rehabilitation in humans with chronic motor complete spinal cord injury

Authors: *S. MESBAH[1], T. PISOLKAR[1], C. A. ANGELI[3], S. J. HARKEMA[4], E. REJC[2]; [1]Kentucky Spinal Cord Res. Ctr., [2]Univ. of Louisville, Louisville, KY; [3]Frazier Rehab Inst., Louisville, KY; [4]Dept Neurol Surgery, Univ. Louisville, Frazier Rehab Inst, KSCIRC, Louisville, KY

Abstract: Individual- and task-specific spinal cord epidural stimulation (scES) parameters can re-enable independent standing (with self-assistance for balance), which is a key achievement toward the recovery of functional mobility, in individuals with chronic motor complete spinal cord injury. The selection of scES parameters for standing is currently performed following dedicated guidelines based primarily on individualized maps of motor pool activation collected in supine position, resulting in an evidence-based process that relies substantially on the operators' expertise. We recently demonstrated that wavelet analysis can provide relevant EMG features contributing to the accurate classification (~96% by K-nearest neighbor) of assisted and independent standing. We also observed that independent standing was promoted by EMG activity characterized by lower median frequency, lower variability of median frequency, lower variability of activation pattern, lower variability of instantaneous maximum power as well as higher total power. In the present study, we initially took advantage of these findings to develop a prediction algorithm capable of ranking effectiveness of muscle activation for standing. We trained muscle-specific KNN models based on data sets related to different external assistance for standing. We then fed the prediction algorithm with 48 standing events performed by 6 individuals while different scES parameters were tested. Ranking scores varied substantially among scES parameters applied and investigated muscles. This approach can identify which muscle groups present poor activation and conceivably limit the achievement of independent standing, thus narrowing down subsequent scES parameters adjustments. Also, it can suggest which of the tested set of scES parameters promotes the activation pattern more effective for standing; this can be relevant when different sets of parameters result in the same need of external assistance for standing, and the decision on which parameters to apply for standing rehabilitation should be made. Additionally, we performed preliminary analysis on supine

stimulation mapping EMG data to determine the effects of scES parameters on time- and frequency-domain EMG characteristics related to standing ability. Preliminary analysis suggests that adjustments in scES parameters result in individual- and muscle-specific adaptations of these EMG characteristics. Future studies should assess whether scES parameters resulting in EMG characteristics more effective for standing during supine stimulation mapping may also promote better standing muscle activation and ability.

Disclosures: S. Mesbah: None. **T. Pisolkar:** None. **C.A. Angeli:** None. **S.J. Harkema:** None. **E. Rejc:** None.

Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.10/I28

Topic: C.11. Spinal Cord Injury and Plasticity

Support: 1OT2OD024898, National Institutes of Health

Title: Regulation of cardiovascular function with epidural stimulation maintains normative blood pressure responses to bladder distension in individuals with chronic spinal cord injury

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Abstract: More than 1.5 million people live with spinal cord injury (SCI) in the USA. Many of them suffer from bladder dysfunction that significantly lowers their quality of life after SCI. Neural control of micturition requires complex coordination between supraspinal centers, autonomic (sympathetic and parasympathetic) and somatic (pudendal) pathways. Supra-sacral SCI disrupts voluntary and autonomic control of bladder function resulting in detrusor over-activity and uncoordinated bladder and external urethral sphincter contractions characterized by low overall compliance (low bladder capacity under high detrusor pressure). Furthermore, SCI above T6 can disrupt sympathetic control of the heart and the blood vessels, impairing cardiovascular autonomic regulation of blood pressure (BP) consistent with persistent hypotension and/or episodes of uncontrolled hypertension known as autonomic dysreflexia (AD). Both neurogenic bladder and cardiac autonomic impairment places individuals with cervical and upper-thoracic SCI at considerable risk for AD and, long-term cardiovascular diseases. Recently, we demonstrated that lumbosacral spinal cord epidural stimulation (scES) optimized for cardiovascular function restored autonomic cardiovascular function in individuals with cervical SCI. In this study, we investigated the effects of scES optimized for cardiovascular

and bladder storage function on BP responses in individuals with cervical and upper-thoracic SCI. Optimal scES configurations were identified to promote both the neural control of bladder storage and the maintenance of normative BP. Initial studies were conducted in two participants (AIS B; C4 and T2 levels of injury). Continuous BP and heart rate using the non-invasive BP monitoring system were acquired during cystometry (bladder filling) without scES at baseline and with scES, over a 5-month period. In addition, the first participant received scES training at home. Blood pressure was greater than 160/80 mmHg in both individuals at baseline and decreased to 120/78 mmHg and 110/65 mmHg, respectively, during urodynamics. Both individuals reported decreased or no AD symptoms during bladder filling when scES was in use. Moreover, improved control of BP regulation facilitated a further increase in bladder capacity, within normative range of 400-450 ml (per International Continence Society guidelines) with scES during cystometry. In conclusion, scES has potential to improve BP during bladder filling in individuals with SCI and reduce the number of daily catheterizations, which may improve their quality of life and lead to a decrease in the morbidity and mortality risk.

Disclosures: S.C. Aslan: None. **A.N. Herrity:** None. **C. Hubscher:** None. **S.J. Harkema:** None.

Poster

481. Chronic Spinal Cord Injury

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ES_BI-2017, Christopher and Dana Reeve Foundation
ES2-CHN-2013, Craig H. Neilsen Foundation

Title: Effects of epidural spinal cord stimulation on respiratory motor function in individuals with chronic spinal cord injury

Authors: *A. V. OVECHKIN[1], B. DITTERLINE[1], S. C. ASLAN[1], C. A. ANGELI[2,1], S. HARKEMA[2,1];
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Abstract: Introduction: Respiratory and cardiovascular complications are listed as the leading causes of morbidity and mortality in individuals with chronic spinal cord injury (SCI). However, there is no clinical standard of care that has been established for individuals with these abnormalities. Respiratory and cardiovascular systems are inter-related and impact one another through respiratory-cardiovascular (also known as cardio-respiratory) coupling mechanisms. We

demonstrated that lumbosacral spinal cord epidural stimulation specifically configured to target cardiovascular function (CV-scES) can normalize the arterial blood pressure in individuals with SCI-induced cardiovascular deficits. We hypothesized that cardiovascular effects of the CV-scES are associated with respiratory modulations.
Methods: In six individuals with motor-complete SCI above T4, Spirometry (Forced Vital Capacity /FVC/; Forced Expiratory Volume in 1 sec /FEV_1/; Maximum Inspiratory and Expiratory Pressure /PI_{max} and PE_{max}/; and surface electromyography of upper trapezius, intercostal, rectus abdominus, and oblique muscles have been obtained with CV-scES "off" or "on" both at baseline and after 80 sessions of CV-scES.
Results: In response to stimulation, the participants demonstrated no acute changes in spirometrical and electromyographic outcomes. However, after exposure to 80 sessions of CV-scES, specifically configured to target the arterial blood pressure regulation, there were increase in spirometric measures in association with improved respiratory multi-muscle activation patterns.
Conclusion: These results indicate that CV-scES facilitates respiratory-cardiovascular remodeling within spinal autonomic and motor networks. This intervention may be used as a therapeutic option to improve respiratory-cardiovascular health in patients with SCI.

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Poster

481. Chronic Spinal Cord Injury

Location: Hall A

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Program #/Poster #: 481.12/I30

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ES2-CHN-2013, Craig H. Neilsen Foundation, Christopher and Dana Reeve Foundation
ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Improved cardiac and circulatory function after epidural stimulation of the lumbosacral spinal cord

Authors: *B. DITTERLINE[1], S. WADE[1], B. UGILIWENEZA[1], N. SINGAM[2], S. J. HARKEMA[1], M. STODDARD[2], G. A. HIRSCH[3];
[1]Kentucky Spinal Cord Injury Res. Ctr., [2]Div. of Cardiovasc. Med., Univ. of Louisville, Louisville, KY; [3]Div. of Cardiol., Natl. Jewish Hlth., Denver, CO

Abstract: Introduction: Spinal cord injury (SCI) results in profound cardiovascular dysfunction that results in persistent hypotension, orthostatic hypotension, and autonomic dysreflexia. Spinal

cord epidural stimulation (scES) has demonstrated the ability to acutely increase hypotensive blood pressure to a normal range and mitigate orthostatic hypotension even without stimulation. However, effects of scES on the heart are unknown. We sought to understand how the heart acutely responds to scES, and the role it plays in maintaining blood pressure after an scES intervention.Methods: Nine individuals with chronic, cervical SCI were included. Individuals were implanted with a stimulator over spinal segments L1-S1. Individual-specific scES configurations (electrode polarity, amplitude, frequency, and pulse width) were identified to maintain systolic blood pressure within 107-120 mmHg (CV-scES) without skeletal muscle contraction. Blood pressure was confirmed with brachial measurements. Echocardiography was performed before and after scES training by a registered diagnostic cardiac sonographer in the left-lateral decubitus position and while seated at a 45-degree incline to create a mild orthostatic stress.Results: Application of CV-scES increased blood pressure in the seated position and led to rapid increases in cardiac output, end diastolic volume, and systolic flow in the hepatic veins. There were also rapid increases to VTI of blood measured in the LVOT, ascending aorta, and descending aorta. After a prolonged scES intervention, measured without stimulation, there were significant increases to ejection fraction, end diastolic volume, LVOT VTI, and LV Mass. Despite increased mean arterial pressure and increased afterload, there were no increases to end systolic volume and stroke volume remained the same.Conclusions: Acute CV-scES rapidly increased venous return to the heart, increasing end diastolic volume and cardiac output during orthostatic stress. VTI of blood in the LVOT and ascending and descending aorta also rapidly increased. This indicates acute CV-scES promotes redistribution of blood from the capacitance vessels into the systemic circulation. After a prolonged scES intervention, even without stimulation, there were significant increases to ejection fraction, end diastolic volume, LVOT VTI, and LV mass, and no changes to end systolic volume. This indicates scES can lead to beneficial changes within the heart that improve cardiovascular function, which can lead to improved cardiovascular regulation.

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Poster

481. Chronic Spinal Cord Injury

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Program #/Poster #: 481.13/I31

Topic: C.11. Spinal Cord Injury and Plasticity

Support: ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Subthreshold spinal cord epidural stimulation acutely restores voluntary movement control in individuals with motor complete spinal cord injuries

Authors: *J. M. D'AMICO[1], S. J. HARKEMA[1,2], E. REJC[1], C. ANGELI[2,1];
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Abstract: Following human spinal cord injury (SCI) there is a marked interruption in descending inputs to the spinal cord which results in reduced voluntary motor activity and impaired motor function. However, the spinal cord can recover and exhibits considerable plasticity at various levels of the motor pathway. Because most human SCI are not anatomically complete, recovery of function most likely involves plasticity in circuitry above and below the lesion. Through the use of epidural stimulation (scES) and task-specific training we have provided a cellular environment that enables sensory-motor circuits to recover significant levels of function. The purpose of this study was to investigate whether subthreshold scES alone, prior to training, can restore voluntary activation below the lesion. Seven participants (33±13 years of age) with chronic motor complete SCI (5.3±2.8 years since injury) who were unable to voluntarily move their legs were implanted at L1-S1 with an electrode array and neurostimulator. Three initial sessions of spatiotemporal neurophysiological mapping and voluntary movement mapping was performed to determine the optimal stimulation configuration to elicit hip flexion, ankle dorsiflexion and hallux extension. Different configurations were used for each leg. Participants then performed a functional neurophysiological assessment which consisted of standardized mono-articular movements (unilateral hip flexion and extension, knee extension, ankle dorsi and plantar-flexion, hallux extension) in a supine position with and without delivery of scES. Surface EMG was recorded from sixteen lower limb muscles while participants were instructed to perform three attempts of each movement. EMG activity was detected in the agonist muscles during hip flexion (left: 33±13% of attempts, right: 43±19%), ankle dorsiflexion (left: 33±16%, right: 48±15%) and hallux extension (left: 43±16%, right: 38±17%). Interestingly, EMG activity was also detected in the appropriate agonist muscles during hip extension (left: 22±16%, right: 50±20%), knee extension (left: 50±15%, right: 28±12%) and ankle plantarflexion (left: 28±17%, right: 56±17%). These results indicate that subthreshold epidural stimulation can sufficiently alter the central state of excitability of the spinal cord to allow residual voluntary inputs to effectively elicit muscle activity below a complete spinal cord injury, even in the absence of training. Interestingly, it appears that even subthreshold scES that was not mapped for a specific movement can effectively restore voluntary control below a lesion.

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Poster

481. Chronic Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

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2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust
ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Correlation of radiographic spinal cord parameters with volitional movement after spinal cord epidural stimulation for chronic traumatic spinal cord injury

Authors: *T. BALL, C. ANGELI, E. REJC, S. MESBAH, S. HARKEMA, M. BOAKYE; Univ. of Louisville, Louisville, KY

Abstract: Background
Spinal cord epidural stimulation has been shown to enable volitional lower extremity movement in patients with chronic traumatic spinal cord injuries. The parameters correlating with successful stimulation are still not well understood. In particular, there is sparse literature on the radiographic predictors of success. Our goal in this study was to correlate radiographic parameters with the volitional motor responses post-operatively (number of joints moved)
Methods
For participants with appropriate imaging, we measured the following parameters: 1.) The cross-sectional area (CSA) of the spinal cord at the inferior endplate of C3. 2.) The CSA of the spinal cord at the superior endplate of T12. 3.) The ratio of the CSA of the residual neural tissue to the CSA of the cord at C3 inferior endplate was classified at <1/3, 1/3 to 2/3, or greater than 2/3. 4.) The position of the inferior-most aspect of the stimulator with respect to the inferior-most aspect of the conus medullaris (below, at, or above the termination of the conus medullaris).
Results:
1.) There was a positive correlation between the CSA of the spinal cord at the inferior endplate of C3 and the number of joints moved (R^2 of 0.35).
2.) Placement of the stimulator above the termination of the conus medullaris does not appear to adversely affect the number of joints moved and may be associated with slightly higher efficacy than placing the bottom of the stimulator at of below the termination of the conus medullaris, but this needs to be confirmed with more participants
3.) There is a poor correlation between the C3 CSA and the T12 CSA, and the C3 CSA seems to be a better predictor of number of joints moved.
4.) Even in participants who had less than 1/3 of the normal CSA compared to the normal cord, some were able to achieve a good functional status.
Conclusions:
Careful evaluation of pre-operative radiographic parameters may help identify patients that are more likely to benefit from spinal cord epidural stimulation with regards to regaining volitional movement of the lower extremities.

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Poster

481. Chronic Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: 2016PG-MED001, Leona W and Harry B. Helmsley Charitable Trust
ES_BI-2017, Christopher and Dana Reeve Foundation
ES2-CHN, Craig H Neilsen Foundation

Title: Documentation of clinical benefits of epidural stimulation and proposal of a new multidimensional outcome measure for individuals with spinal cord injury

Authors: *S. KIRSHBLUM[1], C. A. ANGELI[2], J. D. GUEST[3], G. F. FORREST[4], J. WECHT[5], N. Y. HAREL[6], O. BLOOM[7], A. V. OVECHKIN[8], E. REJC[9], S. J. HARKEMA[10];
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Abstract: The ability to regain motor activity, translating to improved functional activity, is extremely important to persons with spinal cord injury (SCI). However, there are many other critically important residua of SCI that significantly impact the health and quality of life of affected persons. These include cardiovascular dysfunction (hypotension and hypertensive episodes), thermoregulatory, respiratory, bowel, bladder, and sexuality related dysfunction as examples of what is often referred to as the “hidden impairments” of SCI. To date, 20 individuals with motor complete injury have undergone spinal cord epidural stimulation (scES) and training at one center. Results to date (either by defined tools (“measured”) or by patient report (“reported”) have shown improvements in respiratory function (n=16, measured); cardiovascular function (n=12, measured, n=17 reported); bladder and bowel function to varying degrees (n=18, reported; n=8, measured); improved temperature regulation and sweating (n=17, reported); improved cognition and alertness/well-being (n=9, measured; n=16 reported) and sexual function (n=4, reported). These results reveal benefits of scES in numerous domains of medical disturbances after SCI. However, to document improvement in each of these requires application of several scales which can create patient burden while still not fully capturing the significance of improvement in overall health and its impact on quality of life or activities of daily living. As such, a new measure linking different domains of physiological function is being developed that will document quantitative and patient-reported outcomes that can be used prospectively to

gauge an overall 'health profile' of persons with SCI. This poster will present both the medical benefits of scES to date on 20 implanted patients as well as the new measure developed for future use.

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Poster

481. Chronic Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

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ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Lumbosacral spinal cord epidural stimulation acutely improved cerebral blood flow regulation during orthostatic stress after chronic human spinal cord injury

Authors: *S. WANG[1], J. M. WECHT[2], A. V. OVECHKIN[1], B. DITTERLINE[1], J. D. GUEST[3], G. F. FORREST[4], O. BLOOM[5], S. J. HARKEMA[1,6];
[1]Kentucky Spinal Cord Injury Res. Ctr., Univ. of Louisville, Louisville, KY; [2]James J Peters VA Med. Ctr., Bronx, NY; [3]Neurolog. Surgery/Miami Project to Cure Paralysis, Univ. of Miami Miller Sch. of Med., Miami, FL; [4]Kessler Fndn., West Orange, NJ; [5]The Feinstein Inst. For Med. Res., Manhasset, NY; [6]Frazier Rehab Inst., Louisville, KY

Abstract: Introduction: Severe spinal cord injury (SCI) causes cardiovascular dysfunction including orthostatic hypotension. As a result, cerebral hypo-perfusion can cause dizziness and lightheadedness and may be associated with decline of cognitive function and increased risk of stroke. We previously showed that epidural stimulation at lumbosacral spinal cord (scES), targeted for cardiovascular function (CV-scES), acutely and consistently mitigated orthostatic hypotension in individuals with chronic SCI. The goal of this study is to evaluate the acute effect of CV-scES on cerebral blood flow (CBF). **Methods:** Individuals (n=5) with chronic cervical motor-complete SCI and cardiovascular deficit were implanted with a 16-electrode array on the dura (L1-S1 cord segments, T11-L1 vertebrae). Specific CV-scES configurations (anode and cathode electrode selection, amplitude, frequency, and pulse width) for each individual were identified to maintain systolic blood pressure within a targeted normative range without lower extremity muscle activity. Orthostatic tolerance was tested with a 70°- head-up tilt maneuver lasting for 30 minutes until symptoms limited. Transcranial Doppler was used to assess CBF in

the middle cerebral artery, with simultaneous blood pressure and heart rate monitoring at supine and during the head-up tilt maneuver. The tilt test was performed without CV-scES and repeated with CV-scES. Beat-to-beat mean arterial pressure (MAP) and mean CBF velocity (mCBFv) were analyzed. Cerebrovascular conductance, as a measure of cerebral vasodialation, was estimated as mCBFv/MAP. Cerebrovascular autoregulatory function during tilt was estimated as the regression coefficient between mCBFv and MAP during MAP decline. **Results:** Orthostatic tolerance increased with CV-scES (duration of tolerated tilt: 30 ± 0 minutes) compared to without CV-scES (5.5 ± 3.9 minutes). Decreases in MAP (-12 ± 14 mmHg, 13 ± 14%) and CBFv (-4 ± 8 cm/s, 9 ± 20%) from supine to tilt with CV-scES were reduced compared to without CV-scES (-37 ±11 mmHg, 47 ± 12% and -17 ± 7 cm/s, 32 ± 10% respectively). Cerebrovascular conductance during tilt with CV-scES was unchanged from supine (104 ± 9 %) as compared to an increase during tilt without CV-scES (137 ± 47 %). The regression coefficient between mCBFv and MAP during tilt was 0.29 ± 0.19 cm/s/mmHg with CV-scES and 0.71 ± 0.36 cm/s/mmHg without CV-scES. **Conclusions:** Acute CV-scES increased orthostatic blood pressure and CBFv and improved orthostatic tolerance in individuals with chronic SCI. Cerebral vasodialation was restored to supine level, and cerebrovascular autoregulatory function was improved with CV-scES during orthostatic stress.

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Poster

481. Chronic Spinal Cord Injury

Location: Hall A

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Program #/Poster #: 481.17/I35

Topic: C.11. Spinal Cord Injury and Plasticity

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2016PG-MED001, Leona M. & Harry B. Helmsley Charitable Trust

Title: Expanding target range boundaries: A new measure to evaluate continuous blood pressure stability in individuals with chronic spinal cord injury

Authors: *B. UGILIWENEZA[1], S. MESBAH[4], A. N. HERRITY[2], S. C. ASLAN[5], S. WANG[3], S. J. HARKEMA[6];
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Univ. of Louisville, Louisville, KY; [6]Dept Neurol Surgery, Univ. Louisville, Frazier Rehab Inst, KSCIRC, Louisville, KY

Abstract: Profound dysfunction of the cardiovascular system occurs after spinal cord injury (SCI), particularly in motor complete injuries above T6, which is a leading cause of death in this population. Cardiovascular dysregulation leads to persistent hypotension, bradycardia, orthostatic hypotension and episodes of autonomic dysreflexia, which drastically impacts quality of life by affecting overall health and disrupting the ability to engage in daily activities. Our recent work has demonstrated that spinal cord epidural stimulation (scES), in the absence of descending input, can modify the excitability of the relevant spinal interneuronal pools allowing them to respond to peripheral autonomic input and approximate normal cardiovascular control. Current measures of cardiovascular function are limited, as they only focus on a static window of clinically recommended values. Therefore, there is a critical need to identify a sensitive measure that comprehensively captures the dynamic variability that participants experience in their day-to-day life and the effect of scES on blood pressure stability. In this study, our goal was to define and validate a measure of expanding target range boundaries that would quantify the stability of blood pressure within normative ranges as well as account for deviations outside of that range. Using the theory of cumulative density function, the expanding target range boundaries were defined as: 1) the percentage of systolic blood pressure values falling within clinically recommended ranges, and 2) the percentage of values occurring in symmetrically expanded boundary domains, above and below the clinically recommended range. Representation of range distribution and percentage of values within each range was calculated as area under the curve (AUC), distinguishing those individuals with a high percentage of values falling within recommended blood pressure ranges during scES targeting cardiovascular function. We demonstrated that this measure is valid (i.e. discriminatory, reliable and responsive) and was effective at evaluating the level of blood pressure variability and deviations from clinically recommended values in participants receiving scES optimized for cardiovascular function. This measure will improve our understanding of the cardiovascular profile in individuals with chronic SCI and represents a novel method to comprehensively and objectively quantify the effect of scES and training on the cardiovascular system.

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Poster

481. Chronic Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

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1OT2OD024898, National Institutes of Health
ES_BI-2017, Christopher and Dana Reeve Foundation

Title: Human spinal circuitry can integrate somatic-visceral functions with neuromodulation in individuals diagnosed with motor complete spinal cord injury

Authors: *S. J. HARKEMA[1,3], Y. GERASIMENKO[4,1], A. N. HERRITY[2], C. HUBSCHER[5], E. REJC[2], C. A. ANGELI[3,1];
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Abstract: In the past few years, the use of epidural stimulation (scES) in individuals with clinically diagnosed motor complete spinal cord injury has been expanded from motor control to autonomic regulation, both of the cardiovascular system as well as bladder control. Although scES needs to be task-specific and integrated with training for prolonged effects to develop, more than one training intervention can be beneficial for the integration of multiple systems. The purpose of this study is to evaluate the integration of various task-specific scES training paradigms and its effects on motor, cardiovascular and bladder systems. We used a 5-6-5 electrode array and stimulator implanted epidurally from L1 - S1 spinal cord in individuals with chronic motor complete (n=4). Individuals underwent multiple training paradigms (motor, cardiovascular and/or bladder) with task-specific scES either concurrently or by adding one system at a time following a long training intervention within a single system. Epidural mapping for each system occurred prior to optimization of stimulation parameters and the beginning of any training. We show evidence that the spinal cord has the capacity to integrate and regulate more than one system following training with task specific scES. The addition of multiple scES training paradigms does not negatively affect previously scES trained systems while showing significant improvements in additionally trained systems. These results demonstrate that networks within the human spinal circuitry can drive motor movement and simultaneously integrate regulatory control of autonomic function. After spinal cord injury these circuits remain intact and are an untapped resource for therapeutic intervention.

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Poster

481. Chronic Spinal Cord Injury

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Topic: C.11. Spinal Cord Injury and Plasticity

Support: JSPS KAKENHI Grant-in-Aid for Scientific Research (B) 16H05037

Title: Development of regenerative therapy for spinal cord injury in dogs

Authors: W. HANYU, *N. FUJITA, J. CHEN, T. TAKEDA, R. NISHIMURA;
The Univ. of Tokyo, Tokyo, Japan

Abstract: Spinal cord injury (SCI) due to various cause such as intervertebral disc disease and trauma is a major neurological disability in dogs and canine SCI can be regarded as spontaneous and translational animal model for human research. Recently, we have established a novel canine MSC adhering to adipocytes in bone marrow (named as bone marrow peri-adipocyte cells, in short, BM-PACs) and developed cell-based regenerative therapy for canine SCI using BM-PACs. *In vitro*, BM-PACs showed superior ability to secrete hepatocyte growth factor (HGF) which possesses powerful healing effects on SCI in response to inflammatory cytokines. When transplanted into intravenously to SCI model nude mice in acute phase, BM-PACs showed homing ability and secrete HGF at the injured site. After transplantation, mice showed significantly better functional recovery and more myelinated areas retained. Further, BM-PACs showed secretion ability of VEGF and chemo-attractant property to CXCL12 upregulating at the SCI site in sub-acute phase. When transplanted intravenously to SCI model in sub-acute phase, cells could also migrate toward the injured site and functional recovery were significantly facilitated. Histological evaluation revelated increase of CD31 and NF-200 positive area at the injured site, which suggested angiogenesis and axonal repairing or regeneration were induced by intravenously transplanted cells. Based on these results, clinical application of cell-based therapy for severe canine SCI using BM-PACs are carrying out and can provide useful outcomes for translational research in similar MSC-based therapies for human SCI. On the other hand, we are also investigating a method to induce BM-PACs into neural cells to develop regenerative therapy for canine chronic SCI. When BM-PACs were cultured in neural differentiation medium after FGF-2 treatment, neuron-like morphological changes and MAP2 expression was enhanced. After neural induction, intracellular Ca^{2+} levels increased by KCl stimulation, thus BM-PACs can generate neuron-like cells possessing electrophysiological function and there is a possibility of cell replacement therapy for canine chronic SCI using these cells.

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Poster

481. Chronic Spinal Cord Injury

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Medical research grant related to traffic accidents from the General Insurance Association of Japan

Title: Evaluation methods for translational research of spinal cord injury

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Abstract: [Background] Translational research develops human therapeutic methods based on data of basic research, and evaluations of the outcome of model animals should be equivalent to those of humans in clinical field. In spinal cord injury (SCI) research, many clinical trials have been performed in recent years, but there is contradiction that the method of outcome-evaluation differs between human and model animals. Our team has also performed translational research on SCI with neural stem cell transplantation. We, therefore, developed multiple evaluation-methods which could be common to animals and humans for scientifically-validated translational research. [Purpose] To establish evaluation-methods of model animals which are equivalent or superior to the clinical evaluation-methods for SCI treatment. [Method] (Animal) Female Black 6J mouse and NOD SCID mouse (Model) Infinite Horizon Impactor, moderate contusional injury on Th10 (Evaluation method) We examined the followings as evaluation method-candidates that can be used in clinical fields. Behavioral assessment: digital footprint, kinematic analysis. Electrophysiological evaluation: motor evoked potential, H reflex. Image evaluation: in vivo MRI tractography. [Results] In behavioral evaluation, parameters equal to or higher than those of human walking test were obtained. In electrophysiological evaluation, electromyography corresponding to human magnetic evoked potential was demonstrated, and H reflex was also performed with good reproducibility including habituation-phenomenon. For MRI, we firstly developed the method for quantifying fibers with in vivo spinal cord tractography by devising fixtures.

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Poster

481. Chronic Spinal Cord Injury

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 481.21/I39

Topic: C.11. Spinal Cord Injury and Plasticity

Support: NIH Grant 1OT2OD024898

Title: Optimizing urinary continence with epidural stimulation after human spinal cord injury

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Abstract: Deficits in urological function after spinal cord injury (SCI) include neurogenic detrusor over-activity and uncoordinated bladder and external urethral sphincter contractions, resulting in inefficient emptying and high bladder pressure. Clinical complications associated with high bladder pressure and chronic catheter use include, urinary tract infections, calculi, bladder cancer, and renal deterioration. Bladder distention also is a primary trigger of autonomic dysreflexia (AD) in individuals with cervical and upper thoracic SCI. Standard of care for bladder dysfunction includes the use of pharmacological agents to promote bladder storage and intermittent self-catheterization for bladder evacuation. However, there is a critical need for a successful treatment that restores normal lower urinary tract function as these management strategies and associated cardiovascular dysregulation, continue to diminish the capacity of the bladder and result in side effects that increase morbidity and mortality. In chronic motor complete SCI, we recently demonstrated that customized spinal cord epidural stimulation (scES) configurations targeted for cardiovascular function improved blood pressure regulation, and scES optimized for bladder emptying improved voiding efficiency. However, the direct effects of targeted scES for bladder storage and the ability to simultaneously regulate rising bladder and blood pressure has not yet been investigated. Thus, our overall goal in this study was to optimize scES for safely maintaining urinary continence and to test the effects of training with scES optimized for bladder function for at-home use. These initial experiments were conducted in two participants (AIS B; C4 and T2 levels of injury) during cystometry with continuous beat-to-beat measurements of blood pressure and heart rate (ADInstruments). Over a period of 4-6 weeks, optimal scES configurations (anode/cathode selection, amplitude, frequency, pulse width) were identified at the lumbosacral level (L1-S1) that promoted both the neural control of bladder storage (capacity) and normalization of blood pressure. While controlling blood pressure, successful bladder storage parameters were obtained for both subjects to date, which included capacity and detrusor pressure during filling within the recommended guidelines of the International Continence Society. Targeted scES for urinary continence provides a means for

mitigating AD associated with bladder distention and improving regular standard time intervals between bladder emptying under safe pressures without pharmacological treatments that have unwanted side-effects.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.01/I40

Topic: D.03. Somatosensation – Pain

Title: Contribution of hypothalamic A11 dopaminergic neurons to pain modulation in the dorsal horn of the spinal cord

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Abstract: Pain signals relayed to the dorsal horn of the spinal cord are subject to extensive modulation by local neurons and by neurotransmitters released from supraspinal nuclei. Hypothalamic A11 dopaminergic neurons project to all levels of the spinal cord and provide the main source of spinal dopamine. Electrical stimulation of the A11 nucleus support the anti-nociceptive effects of dopamine in the dorsal horn of the spinal cord. The aims of the present project were: 1) to test the hypothesis that dopamine inhibits the synaptic transmission from primary nociceptors to lamina I projection neurons; 2) to determine the contribution of A11 dopaminergic neurons to pain modulation in vivo in the spare nerve injury (SNI) model of neuropathic pain. In horizontal spinal cord slices in vitro, the excitatory postsynaptic currents (EPSCs) were recorded from lamina I projection neurons upon stimulation of the L4/L5 dorsal root. The external solution was (in mM): 125 NaCl, 2.5 KCl, 26 $NaHCO_3$, 1.25 NaH_2PO_4**,** 20 glucose), oxygenated with 95/5% O_2/CO_2. The internal solution was (in mM): 125 Cs-methanesulfonate, 10 NaCl, 2 $MgCl_2$, 14 phosphocreatine, 4 Mg-ATP, 0.3 Na-GTP, 10 EGTA, 10 HEPES, 5 mM QX-314, pH 7.2 with CsOH. The Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) were selectively expressed in A11 dopaminergic neurons by injecting pAAV-hSyn-DIO-hM3D(Gq) close to the A11 nucleus in TH-Cre rats subjected to the SNI model of neuropathic pain. After three-four weeks post-injection of the AAVs, DREADDs were activated in vivo by intraperitoneal injection of clozapine-N-oxide (CNO) to increase the activity of A11 dopaminergic neurons. Mechanical sensitivity (g) was assessed with the von Frey anesthesiometer. Dopamine strongly inhibited (by ~70%) the EPSCs recorded from lamina I projection neurons upon stimulation of nociceptive Aδ- and C-fibers. Dopamine increased the paired pulse depression ratio (PPR) of paired EPSCs suggesting a presynaptic effect.

Pharmacological experiments proved that the inhibitory effects of dopamine were mediate by D3 and D4 receptors. Immunohistochemistry analysis showed that DREADDs were selectively expressed in TH positive neurons in the hypothalamic A11 nucleus. Activation of DREADDs in vivo with CNO rescued the mechanical pain threshold by about 40% in the ipsilateral hindpaw, while had no effect on the contralateral hindpaw. Taken together, our data show that dopamine strongly inhibits the synaptic transmission between primary nociceptors and lamina I projection neurons, and suggest that activation of A11 dopaminergic neurons in vivo can rescue the mechanical pain threshold in the SNI model of neuropathic pain.

Disclosures: M. Puopolo: None. **J. Lauzadis:** None. **H. Liu:** None. **M. Nerantzinis:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.02/I41

Topic: D.03. Somatosensation – Pain

Support: CIHR

Title: Sex differences in the link between endogenous pain modulation, resilience, pain unpleasantness and salience

Authors: *S. FIROUZIAN[1,2], N. R. OSBORNE[1,2], J. C. CHENG[1,2], J. A. KIM[1,2], R. L. BOSMA[1], K. S. HEMINGTON[1,2], A. ROGACHOV[1,2], K. D. DAVIS[1,2,3];
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Abstract: Background: A “one-size fits all” approach to pain management fails in part due to individual variability in the brain circuitry associated with pain modulation. The effectiveness of the endogenous pain modulation system can be evaluated by the conditioned pain modulation (CPM) test. CPM may be impacted by an individual’s inherent resilience, the affect and attention-grabbing impact of the conditioning stimulus. Therefore, this exploratory study determined the relationship between CPM capacity and 1) resilience, and 2) pain unpleasantness and salience of the modulating stimulus. We also tested whether there were sex differences in these relationships. **Methods :** Healthy adults (51 female, 55 male) completed the Resilience Scale (25-175 scores) and underwent psychophysical testing. We used a familiarization protocol to determine each subject’s Pain50 (temperature to evoke pain intensity rated 50/100). To evaluate CPM, a thermode on one volar forearm (Medoc, QSense) delivered 10s test stimuli (TS) without (TS1) and concurrent with (TS2) a 100s conditioning stimulus (CS) delivered by a thermode to the other arm. All stimuli were at Pain50. Subjects rated TS and CS pain, and CS

pain unpleasantness and salience from 0-100. CPM was calculated as: [(TS2 pain-TS1 pain)/TS1 pain]x100. Thus, negative scores represent pain inhibition (CPM capacity). **Results:** Subjects exhibited a wide range of scores for resilience (83-175), pain unpleasantness and salience (0-100). Subjects also exhibited a wide range of CPM capacities (-100% to +112.5%), and were grouped into those showing pain inhibition (CPM group, n=53), and those lacking thereof or showing pain facilitation (no-CPM group, n=53). At the whole group level, there was no correlation between CPM and resilience (P>0.05). However in males, CPM scores were negatively correlated with resilience in the no-CPM group, but not in the CPM group. There was no statistically significant relationship between CPM and resilience in females. However, pain unpleasantness and salience of the CS were significantly higher in the no-CPM group compared to the CPM group. **Conclusion:** The unpleasant and attention-grabbing nature of a conditioning stimulus may diminish CPM capacity resulting in low CPM capacity (i.e., pain facilitation instead of inhibition). However, high resilience, a positive attribute inherent to subjects, may serve as a protective factor against further pain amplification; this was observed in males lacking CPM.

Disclosures: S. Firouzian: None. **N.R. Osborne:** None. **J.C. Cheng:** None. **J.A. Kim:** None. **R.L. Bosma:** None. **K.S. Hemington:** None. **A. Rogachov:** None. **K.D. Davis:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.03/I42

Topic: D.03. Somatosensation – Pain

Support: Grants-in-Aid for Scientific Research (KAKENHI) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (grant numbers 26893032 and 16K20080 to Dr. Suto)
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Title: Loss of endogenous analgesia leads to delayed recovery from incisional pain in a rat model of chronic neuropathic pain

Authors: *J. OHTA[1], T. SUTO[2], T. HIROKI[3], H. OBATA[4];
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Abstract: Preceding pain and impaired endogenous analgesia are recognized as risk factors of chronic postsurgical persistent pain (CPSP). It is not clear if restoring endogenous analgesia can prevent CPSP. We have shown that a rat model of chronic neuropathic pain, the spinal nerve ligation model 6 weeks after surgery (SNL6W), shows significantly impaired noxious stimulus-induced analgesia (NSIA). It has also been shown that repeated treatment with amitriptyline, a tricyclic antidepressant can restore the NSIA in SNL6W rats. In the present study, we investigated whether SNL6W rats exhibited persistent pain after plantar incision and the effects of perioperative treatment with amitriptyline on postsurgical pain recovery process in SNL6W rats. The rats underwent right L5 and L6 SNL surgery. A plantar incision was made on the contralateral to the nerve ligation at SNL6W. Paw withdrawal threshold was evaluated with von Frey filament postoperatively. Preliminary experiments confirmed that NSIA reversed by five daily treatment with amitriptyline (10 $mg \cdot kg^{-1} \cdot d^{-1}$) was maintained for at least one week. Perioperative amitriptyline (10 $mg \cdot kg^{-1} \cdot d^{-1}$) was administered for consecutive 13 days (-5 to 7 days after incision). To investigate the role of noradrenergic and cholinergic signals in the spinal dorsal horn, pharmacological antagonism was performed. Noradrenaline and acetylcholine content, and density of neuroaxonal fibers synthesizing them, were analyzed to examine the effects of amitriptyline on spinal neuroplasticity. Recovery of the withdrawal threshold of SNL6W rats to pre-incision values required 28 days after plantar incision, while naive rats recovered within 14 days (POD14; $P < 0.0001$, POD21; $P < 0.0001$, POD28; $P = 0.0047$ vs SNL6W). Intrathecal injection of alpha2 adrenoceptor antagonist (idazoxan) or muscarinic cholinergic receptor antagonist (atropine) decreased the withdrawal threshold on POD14 and 21 in naive rats (idazoxan; POD 14, 21, $P < 0.0001$ vs baseline, atropine; POD 14, $P = 0.0038$ vs baseline), but not in SNL6W rats. Perioperative amitriptyline attenuated the delayed recovery in SNL6W rats (vehicle treated SNL6W; POD 28, amitriptyline treated SNL6W; POD 14), and the effect was antagonized by atropine (POD 14, $P < 0.0001$ vs baseline). The concentration of acetylcholine and its synthetic enzyme were not altered by amitriptyline treatment. Noradrenergic and cholinergic analgesia, which is necessary for normal recovery, is lost in the SNL6W rats. A strategy to enhance endogenous analgesia using antidepressants may help to prevent CPSP in chronic pain patients.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.04/I43

Topic: D.03. Somatosensation – Pain

Support: National Natural Science Foundation of China Grant 81671097

Title: Orofacial inflammation with stress induces hyperalgesia through down-regulation of 5-HT_2 receptors

Authors: *Y. XUE[1], S.-Q. WEI[1], P.-X. WANG[1], E.-Q. LIU[2], R. TRAUB[3], D.-Y. CAO[1]; [1]Xi'an Jiaotong Univ. Col. of Stomatology, Xi'an, China; [2]Xi'an Jiaotong Univ. Hlth. Sci. Ctr., Xi'an, China; [3]Univ. of Maryland Sch. of Dent., Baltimore, MD

Abstract: Aim of Investigation: Patients with temporomandibular disorders (TMD) and fibromyalgia syndrome (FMS) have some similar symptoms, but the mechanism is still unclear. The purpose of this study was to investigate whether the impairment of descending pain inhibition system through down-regulation of 5-HT_{2A} and 5-HT_{2C} receptors in the spinal cord contributes to somatic hyperalgesia induced by orofacial inflammation combined with different patterns of stress. **Methods:** Female Sprague-Dawley rats were ovariectomized and injected subcutaneous with 17-β-estradiol (E2, 50 μg in 100 μL safflower oil) every 4 days. Injection of complete Freund's adjuvant (CFA, 150 μL) into bilateral masseter muscles with to induce orofacial inflammation pain. Three or 11 day forced swim stress (FSS 3d or 11d) and 11 consecutive days of a heterotypic stress protocol were used after injection of CFA. The heterotypic stress protocol comprised 3 stressors randomly arranged included FSS, water avoidance stress (WAS), or restraint stress (RS) each day. Somatic sensitivity was assessed with thermal and mechanical stimulation of the hind paw before (baseline) and after stress. The expression of 5-HT_{2A} and 5-HT_{2C} receptors in the L4-L5 dorsal spinal cord was examined by Western blot. The 5-HT_{2A} receptor agonist TCB-2 (100 μg) or 5-HT_{2C} receptor agonist MK212 (100 μg) were injected intrathecally for 5 consecutive days starting at the last 4 days of stress and 1 day after in the heterotypic group, and beginning one day prior to the 3 day FSS group. **Results:** Orofacial inflammation combined with 11 day FSS induced persistent mechanical hyperalgesia till 15 days after FSS and thermal hyperalgesia for 2 days. The mechanical and thermal hyperalgesia lasted for 43 days and 30 days respectively in the heterotypic stress group. 5-HT_{2A} receptor expression significantly decreased in the heterotypic stress group compared to the control (oil+saline+non-stress) group. The expression of 5-HT_{2C} receptor significantly decreased in the orofacial inflammation with stress groups compared to the control group. Intrathecal injection of 5-HT_{2A} or 5-HT_{2C} receptor agonist blocked both mechanical and thermal hyperalgesia evoked by orofacial inflammation pain combined with 3 day FSS or heterotypic stress in E2 treated rats. **Conclusions:** The impairment of descending pain inhibition system through down-regulation of 5-HT_{2A} and 5-HT_{2C} receptors contributes to somatic hyperalgesia induced by orofacial inflammation combined with stress, indicating that 5-HT_{2A} and 5-HT_{2C} receptors may be potential targets in the treatment of TMD comorbid with FMS.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.05/I44

Topic: D.03. Somatosensation – Pain

Support: National Natural Science Foundation of China Grant 81671097
NIH Grant R01 NR015472

Title: Valproate inhibits stress-induced somatic and visceral pain through up-regulation of 5-HT_{2C} receptor

Authors: G.-Z. XU[1], **Y. XUE**[1], S.-Q. WEI[1], *J.-H. LI[1], R. TRAUB[2], M.-D. WANG[3], D.-Y. CAO[1];
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Abstract: Background: Valproate (VPA), a histone deacetylase inhibitor, is analgesic in clinical and experimental studies, but the mechanisms are still unclear. Chronic stress evokes and exacerbates functional pain syndromes such as fibromyalgia, irritable bowel syndrome (IBS) and temporomandibular disorder (TMD). The present study investigated whether repeated administration of VPA attenuated the somatic hyperalgesia and visceral hypersensitivity evoked by 3 day forced swim stress and whether 5-HT_{2C} receptor in the spinal cord contributed to the anti-hyperalgesia effects of valproate. **Methods:** Subchronic stress was produced by forced swim (FS) for 3 consecutive days (10, 20, 20 min) in female Sprague-Dawley rats. Somatic sensitivity was assessed by thermal withdrawal latency to radiant heat and mechanical withdrawal threshold to von Frey filaments. Visceral sensitivity was assessed via visceromotor response to colorectal distension. The expression of 5-HT_{2C} receptor in the L4-L5 and L6-S1 dorsal spinal cord was examined by Western blot. VPA (300 mg/kg) or its vehicle saline was intraperitoneally injected 30 min before each FS and 1 day after FS for 4 consecutive days. 5-HT_{2C} receptor antagonist RS-102221 (30 μg, 10 μL) was intrathecally injected 30 min after VPA injection in the RS-102221 group. **Results:** Repeated FS significantly reduced the thermal withdrawal latency and mechanical withdrawal threshold, as well induced visceral hypersensitivity in the intraperitoneal injection of saline group. The somatic hyperalgesia and visceral hypersensitivity were accompanied by significant down-regulation of 5-HT_{2C} receptor expression in the L4-L5 and L6-S1 dorsal spinal cord. Intraperitoneal administration of VPA prevented the development of thermal and mechanical hyperalgesia, visceral hypersensitivity, and down-regulation of 5-HT_{2C} receptor in the spinal cord. The reversal of somatic hyperalgesia and visceral hypersensitivity by VPA in FS rats was blocked by intrathecal administration of the selective 5-HT_{2C} receptor antagonist RS-102221. **Conclusion:** VPA attenuated FS-induced somatic hyperalgesia and

visceral hypersensitivity in part by restoring down-regulated function of 5-HT_{2C} receptor in the spinal cord, suggesting that VPA may be a potential drug for the treatment of stress-induced somatic hyperalgesia and visceral hypersensitivity, which are characteristic symptoms of fibromyalgia and IBS, respectively.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.06/J1

Topic: D.03. Somatosensation – Pain

Support: R01DA037621
R01NS45954

Title: Descending serotonergic facilitation of latent pain sensitization is suppressed by μ-opioid receptor constitutive activity in the rostral ventromedial medulla

Authors: *A. H. COOPER, N. S. HEDDEN, B. K. TAYLOR;
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Abstract: Tissue or nerve injury induces latent sensitization (LS) of spinal nociceptive signaling that lasts several months, even after tissue damage and overt signs of hyperalgesia have resolved. Spinal μ-opioid receptor constitutive activity (MOR_{CA}) opposes LS and may prevent the transition from acute to chronic pain (Corder et al, Science, 2013). Opioid receptor inverse agonists unmask LS, leading to pain reinstatement. Hypersensitivity and neuronal activation occur robustly on the side contralateral to injury, suggesting that neuronal sensitization occurs not only at the dorsal horn (DH), but also in the brain. The observation that descending serotonergic projections from the rostral ventral medulla (RVM) facilitate nociceptive processing in the DH forms the premise for the current study. We predicted that inhibition of MOR_{CA} in the RVM would reveal LS and inhibition of $5HT_3$Rs in DH would reduce LS. Adult male C57BL/6 mice underwent hindpaw plantar incision (PI) or sham surgery followed 14 days later by unilateral guide cannula implantation into the RVM. PI induced mechanical hypersensitivity at the plantar hindpaw (tested using the up-down von Frey method) lasting less than 21 days. Following resolution of hypersensitivity, intra-RVM administration of the MOR-selective inverse agonist CTAP (300 ng/0.3 μl) reinstated mechanical allodynia but had no effect in sham-operated mice ($n = 7$; 2-way RM ANOVA with Bonferroni post-tests; $P < 0.05$). This lasted at least 2 hours, with a peak decrease in mechanical threshold occurring 90 mins after injection. In a separate cohort of mice, 21d post-PI, intra-RVM 6β-naltrexol (a neutral opioid receptor

antagonist; 3 µg/ 0.3 µl), abolished intra-RVM CTAP-induced reinstatement of mechanical allodynia but had no effect by itself (n = 8; $P < 0.001$); this demonstrates that a ligand-independent MOR_{CA} mechanism, rather than opioid peptide signaling, suppresses LS in the RVM. We also tested whether descending serotonergic facilitation, mediated by spinal 5-HT_3R signaling, drives LS. 21 days after PI, intrathecal administration of the 5-HT_3R antagonist ondansetron (10 µg/5 µl) attenuated systemic naltrexone-induced reinstatement at both the ipsilateral and contralateral hindpaw ($P < 0.01$, n = 5-7). Ondansetron had no effect in sham-operated mice or in those that did not receive systemic naltrexone ($P > 0.05$). We conclude that inhibition of MOR_{CA} unmasks descending serotonergic $5HT_3$R-mediated facilitation of spinal dorsal horn neurons, leading to pain reinstatement. We propose that descending serotonergic projections from the RVM may be a target for therapeutic intervention to prevent the transition from acute to chronic pain.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.07/J2

Topic: D.03. Somatosensation – Pain

Support: NIH Grant AG053783
NIH Grant DE027808

Title: Age and sex effects on brain connectivity during diffuse noxious inhibitory control (DNIC) in rats

Authors: *C. TRICOU, J. T. DA SILVA, Y. ZHANG, D. A. SEMINOWICZ, J. Y. RO; Univ. of Maryland, Sch. of Dent., Baltimore, MD

Abstract: Typically, endogenous pain modulatory systems are less efficient in chronic pain patients. DNIC or conditioned pain modulation (CPM) is a form of endogenous pain modulation. CPM is compromised in the elderly population, making them more vulnerable to chronic pain conditions. Sex differences in CPM have also been reported, though inconsistently. In any case, neurobiological mechanisms underlying age and sex differences in CPM are relatively unknown. In this study, we used a DNIC behavioral assay and resting state functional magnetic resonance imaging (rsfMRI) to assess the effect of age and sex on endogenous pain modulation and related brain circuitry in rats. Groups of male and female Fischer 344 rats, consisting of both young (3-6 mo) and aged (20-24 mo) rats were used. DNIC was assessed with capsaicin in the forepaw as the conditioned stimulus and noxious heat on the hindpaw as the test stimulus. Changes in thermal thresholds before and 15, 30, 60, 90, and 120 min after capsaicin treatment were

assessed. For rsfMRI, rats were scanned using a Bruker 7T MRI and under isoflurane anesthesia ≤ 1.5%. Functional scans (TR = 1500 ms, in plane resolution = 400 μm, slice thickness 1 mm) were acquired 15 min before and 45 min after the capsaicin treatment. rsfMRI scans were analyzed to examine the effects of DNIC on anterior cingulate cortex (ACC) connectivity to the whole brain. Young males exhibited stronger DNIC responses than young females. DNIC responses were significantly impaired in both old male and old female rats. Young males' greater DNIC responses were associated with strong PAG-ACC connectivity, while young females strongly engaged circuitries implicated in the noradrenergic descending pain modulation, such as the retrosplenial cortex (Rs), pontine nuclei (Pn), and locus coeruleus (LC). The decreased DNIC responses in old females were associated with greater ACC connectivity to the PAG and the limbic system. Comparisons in ACC connectivity between young males and old males did not show statistical differences, suggesting that deficient DNIC responses in old males may involve brain structures other than ACC. Our findings showed that DNIC and brain networks are modulated in age- and sex-dependent manners. Sex differences in DNIC primarily involved connectivity of ACC-PAG whereas age differences in DNIC were associated with the limbic system and other distinct brain areas.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.08/J3

Topic: D.03. Somatosensation – Pain

Support: COBRE award P20GM103643

Title: Differential endogenous pain inhibition between male and female rats contribute to sex differences in development of temporomandibular joint osteoarthritis pain

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Abstract: Males rats develop chronic ongoing pain and central sensitization at a five-fold higher dose of monosodium iodoacetate (MIA) than females in a model of temporomandibular joint osteoarthritis (TMJOA). We propose that this sex difference in susceptibility to development of ongoing pain and central sensitization are due to differences in descending pain inhibition. A measure of endogenous pain inhibition used in the clinical and preclinical setting is diffuse

noxious inhibitory control (DNIC), also referred to in humans as conditioned pain modulation (CPM). This measure demonstrates analgesia to a noxious stimulus in the presence of a secondary noxious stimulus applied elsewhere on the body. We assessed hindpaw analgesia to noxious mechanical stimulation induced by forepaw capsaicin injections to measure CPM in male and female Sprague Dawely rats. Rats received left TMJ injection of high (80 mg/ml, males only) or low (16 mg/ml, males and females) concentrations of MIA or equivolume saline (50 μl). Day 14 post-injection, rats were tested for capsaicin-induced mechanical analgesia (CPM) using the Randel Silletto test. Baseline withdrawal thresholds to noxious mechanical stimulation of the hindpaw were recorded followed by an intraplantar injection of capsaicin (125ug/ 50ul) into the right forepaw under light isoflurane anesthesia. Paw withdrawal thresholds were again measured 15, 30, 45, and 60 minutes post-capsaicin. Saline-treated males demonstrated longer-lasting capsaicin-induced analgesia compared to female rats. MIA diminished capsaicin-induced analgesia in a dose dependent manner in the male rats. To determine whether endogenous opioids protect males from low dose MIA-induced TMJOA pain, we assessed whether systemic naloxone (3 mg/kg, i.p.) induced conditioned place aversion (CPA) and FOS expression in the medullary dorsal horn. Our results demonstrate that naloxone produces CPA and FOS expression in the medullary dorsal horn of low-dose MIA treated males and not in saline treated controls. In conclusion, male rats show stronger capsaicin-induced analgesia compared to females and naloxone unmasked TMJOA pain resulting in CPA and FOS expression in the medullary dorsal horn of low-dose MIA treated male rats. These observations indicate that endogenous opioids protect male rats from developing TMJOA-induced ongoing pain. These findings suggest that males and females inherently differ in descending pain modulation with males having stronger descending pain inhibitory systems than females and that blocking endogenous opioids in males unmasks TMJOA-induced pain. This research was supported by a COBRE award (P20GM103643).

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.09/J4

Topic: D.03. Somatosensation – Pain

Support: FIPE-HCPA #140635

Title: Evaluation of descending endogenous pain-modulating system in daughters of patients with fibromyalgia

Authors: *L. F. MEDEIROS[1,2], R. MUNIZ[2], R. H. PALUDO[2], J. DUSSAN-SARRIA[1], W. CAUMO[1], A. SOUZA[2];
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Abstract: Introduction: fibromyalgia syndrome is characterized by pain and widespread sensitivity, neural changes, and alterations in the peripheral and the central physiology mechanisms. This syndrome can be related with genetic, neurobiological and environmental factors. It is known that, in different chronic pain processes, descending modulation of pain pathways can present some dysfunctions. The Conditioned Pain Modulation (CPM) task has been used to assess the descending endogenous pain-modulating system in clinical research field. And, data from literature has described the role of the brain-derived neurotrophic factor **(**BDNF) in the maintenance mechanism, sucha as survival, growing, neuroplasticity, neural reparation, and neuronal differentiation, and also in the pain process mechanisms. Thus, our objective was to characterize differences in the pain response between case and control groups, which consisted by daughters of fibromyalgia patients and daughters of women pain-free, respectively. Methods: this is a case-control study, approved by IRB#140635. Seventy-six women were enrolled after signed the informed consent form, 38 daughters of patients with fibromyalgia diagnosis (case group), and 38 daughters of women without this syndrome (control group). Psychophysical tests were: pain threshold by quantitative sensory testing (QST) and conditioned pain modulation (CPM). Sociodemographic questionnaire was applied and blood serum sample was collected. BDNF (ng/ml) and estradiol (pg/ml) serum levels were measured. Data were analyzed by SPSS; $P<0.05$ was considered significant and considering the non-normal distribution data, Mann-Whitney test was used. Results: no differences were found in BDNF and estradiol serum levels between case and control groups ($P>0.05$). However, we found interesting results, the case group presented lower delta response in CPM-task than control group taking into account levels of BDNF and estradiol ($P<0.05$), suggesting a descending endogenous pain-modulating system less efficient. Conclusion: our results showed that the case group already presents changes in the descending endogenous pain-modulating system assessed by CPM. Important to highlight that all women enrolled in the current study were healthy (without fibromyalgia syndrome). And, further studies needs to be encouraged to analyze possible changes in pain modulation mechanisms in daughters of fibromyalgia patients, for example, a cohort design study.

Disclosures: L.F. Medeiros: A. Employment/Salary (full or part-time):; La Salle University. **R. Muniz:** None. **R.H. Paludo:** None. **J. Dussan-Sarria:** None. **W. Caumo:** None. **A. Souza:** A. Employment/Salary (full or part-time):; Universidade La Salle.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.10/J5

Topic: D.03. Somatosensation – Pain

Support: European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No.642720
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Title: Cancer-induced bone pain: Peripheral and central mechanisms in the rodent models of the disease

Authors: *M. W. KUCHARCZYK[1], A. DICKENSON[2], S. MCMAHON[1], K. BANNISTER[1];
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Abstract: Cancer pain remains a major area of unmet medical need. One common form of chronic cancer pain, affecting 400,000 people each year in the US alone, is associated with skeletal metastases. These pains are typically mechanoceptive in nature and poorly managed by available analgesics. Here, we employed *in vivo* imaging using GCaMP6s to assess the properties of the nerve fibres that transduce bone cancer pains. We show that a subclass of nociceptors, those that are normally mechanically insensitive, are recruited and activated in a rodent model of bone cancer, and that this dramatically increases sensory input from the diseased tissue to the central nervous system. The recruitment of these so-called silent afferents was shown to be Piezo2-dependent.
Next, utilising *in vivo* spinal electrophysiology, we show that the increased peripheral input described above leads to the reorganization of descending noradrenergic controls, potently increasing inhibitory tone. We hypothesise the existence of a spino-pontine-spinal loop that modulates spinal excitability in a noradrenergic fashion and is strongly altered in the advanced metastatic disease. This changes the spinal pharmacology of α_2-adrenoceptor antagonist atipamezole, which now has inhibitory actions at the level of the spinal cord.
Diffuse Noxious Inhibitory Controls (DNIC), a unique form of descending noradrenergic controls, was studied also. This phenomenon, whereby application of a noxious stimulus to one part of the body inhibits pain perceived in a remote body region, acts through inhibitory descending pathways. Interestingly, DNIC were found dynamic with the progression of bone tumours. We hypothesise that DNIC originate from brain regions separate to those that govern tonic noradrenergic controls, and we conclude that the expression status of DNIC can be used clinically as a diagnostic tool to tailor pain pharmacotherapy in patients suffering from chronic bone cancer pain.
The unique properties of bone silent afferents, which show plasticity in pain chronicity, combined with ensuing central events offer several novel opportunities for targeting metastatic bone pain. Due to the dynamic nature of the disease and resulting pains, it is crucial to match pain therapy with the stage of the disease.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.11/J6

Topic: D.03. Somatosensation – Pain

Support: Kakenhi 17K09042, 18H02722, 19H04759, 19K16932

Title: Characterization of the widespread sensitization in trigeminal nerve-mediated inflammatory pain model of rats

Authors: *M. YAJIMA, M. SUGIMOTO, Y. K. SUGIMURA, Y. TAKAHASHI, F. KATO; Dept. of Neurosci., Jikei Univ. Sch. of Med., Tokyo, Japan

Abstract: Ectopic/widespread sensitization, an augmented nociceptive sensitivity in (multiple) parts of the body distinct from the site of primary injury or inflammation, is one of the hallmark symptoms of the chronic/centralized pain. It is generally assumed that plastic changes in the central nervous system for processing and controlling the pain-associated signals underlie this symptom, which would provide the basis for "primary chronic pain" (ICD-11, 2018), a type of chronic pain without apparent causes of pain. We have already demonstrated that pharmacological degeneration of the spinal noradrenergic terminals (Kinoshita et al., 2014), artificial activation of the right central amygdala (CeA) neurons (Sugimoto et al., 2016) and orofacial inflammation (Sugimoto et al., 2016) lead to mechanical allodynia in the bilateral hind limbs, suggesting that aberrant perturbation of the ascending and descending pain regulatory loop causes wide-spread sensitization. Using this orofacial inflammation model in rats, we characterized the mechanisms underlying this sensitization. Injection of formalin into the upper lip lowered the paw withdrawal threshold (PWT) in bilateral hind limbs, lasting for >72 hours. Administration of acetaminophen (100-200 mg/kg, i.p.) at 3.5 h post-formalin elevated the PWT to levels not significantly different from the pre-formalin level. This effect of acetaminophen lasted for ~6 h. As recent lines of evidence suggest acetaminophen exerts its analgesic effects by indirectly activating endocannabinoid receptors (Klinger-Gratz et al, 2018), it is suggested that the widespread sensitization following orofacial inflammation would involve up-regulation of the descending pain modulatory system from the CeA to the spinal dorsal horn, which is under control by endocannabinoids and CB1 receptors.

Disclosures: **M. Yajima:** None. **Y. Takahashi:** None. **Y.K. Sugimura:** None. **F. Kato:** None. **M. Sugimoto:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.12/J7

Topic: D.03. Somatosensation – Pain

Title: Resting brain connectivity underlying conditioned pain modulation analgesia

Authors: *E. P. MILLS[1], A. M. YOUSSEF[1], P. M. MACEY[2], L. A. HENDERSON[1]; [1]Univ. of Sydney, Sydney, Australia; [2]UCLA Sch. of Nursing, Univ. of California at Los Angeles, Los Angeles, CA

Abstract: Conditioned pain modulation (CPM) is an analgesic mechanism where pain at one site is inhibited by a second, remote, noxious stimulus. It is important to understand why some individuals express CPM analgesia and others do not. Indeed, the risk of developing chronic pain is greater in individuals with reduced CPM abilities, suggesting that resting activity within CPM neural circuits predisposes an individual to developing chronic pain. We have shown that the subnucleus reticularis dorsalis (SRD) in the medulla is important for CPM in humans. In the present study, we used functional magnetic resonance imaging (fMRI) to explore whether CPM ability is related to the strength of resting SRD signal coupling with other pain-modulation regions. We recruited 46 healthy subjects (19 males; mean[±SEM] age: 34±2 years). First, we applied 8 noxious thermal stimuli to the subject's forearm using a 3x3cm thermode (Medoc, Israel) (*test stimulus, TS*). The subject rated their pain intensity to each TS (0=no pain, 10=worst pain imaginable) using a Computerised Visual Analogue Scale (Medoc). After the fourth stimulus, the subject immersed their foot in noxious cold water (*conditioning stimulus, CS*) and continued to rate pain evoked by the TS. Based on the change in pain ratings during simultaneous TS and CS compared to those during TS alone, subjects were grouped as either showing CPM analgesia ("CPM"; n=22) or no CPM analgesia ("NoCPM"; n=24). Additionally, each subject underwent a 6-minute resting state fMRI scan. Using SPM12, fMRI images were realigned, physiological noise removed and the brainstem spatially normalized to a brainstem-only template using the SUIT toolbox. The SRD was selected as a "seed" region in a functional connectivity analysis using the DPARSF toolbox. Using the brainstem-only and whole-brain images separately, the SRD connectivity with each voxel was compared between CPM and NoCPM subjects in voxel-by-voxel analyses ($p<0.05$, small volume corrected). Compared to the NoCPM group, CPM subjects showed significantly greater resting SRD functional connectivity with the spinal trigeminal nucleus (mean[±SEM] connectivity strength in arbitrary units, CPM: 0.32±0.03, NoCPM: 0.15±0.04). Further, CPM participants demonstrated greater SRD connectivity with higher regions involved in modulating pain, including the mid-cingulate cortex (CPM: 0.12±0.02, NoCPM: -0.02±0.03). The results suggest that resting connectivity between pain-modulation areas underlies an individual's ability to engage analgesic mechanisms during

two noxious stimuli. This may confer a protective advantage in CPM individuals that reduces their likelihood of developing chronic pain.

Disclosures: E.P. Mills: None. **A.M. Youssef:** None. **L.A. Henderson:** None. **P.M. Macey:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

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Program #/Poster #: 482.13/J8

Topic: D.03. Somatosensation – Pain

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Title: Descending control of the spinal lamina X neurons

Authors: *V. KROTOV[1,2], K. AGASHKOV[2], B. V. SAFRONOV[3], P. BELAN[1,4], N. VOITENKO[2,4];
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Abstract: Descending control of the spinal neurons is poorly understood, despite being crucial for the motor and sensory information processing. Since the area around the central canal (lamina X) is the spinal region participating in both these functions, it is interesting to study how descending regulation affects lamina X neurons. For this, we did the patch-clamp recordings in the hemisected spinal cord preparation from P12 rats while stimulating the dorsolateral funiculus and the ipsilateral dorsal root. Such approach allowed investigating the inputs from descending fibers and their impact on the primary afferent-driven responses. We found that more than a half of the tested lamina X neurons responded with polysynaptic EPSCs and/or IPSCs to a single descending tract stimulation. The putative monosynaptic inputs were rare, suggesting little direct synaptic contacts between descending fibers and lamina X neurons in young animals. Meanwhile, in a number of neurons continuous activation of the descending fibers (2-10 Hz) diminished mono- and polysynaptic components of the primary afferent input evoked by the dorsal root stimulation. Taken together, these findings indicate that descending regulation of the spinal lamina X circuitry involves both pre- and postsynaptic mechanisms.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.14/J9

Topic: D.03. Somatosensation – Pain

Support: U of A Start-Up

Title: PEBP detects incoming nociceptive information to enhance endogenous opioid tone from descending inputs

Authors: *J. LAVIGNE[1], C. KIM[2], K. A. EDWARDS[4], J. M. STREICHER[3];
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Abstract: The United States has roughly 100 million people suffering from chronic pain, which has been poorly managed by opioid treatment with attendant side effect and abuse liabilities. Recent efforts to create novel therapies that avoid these problems are promising, however none have been truly successful. A likely reason for this is due to a lack of understanding of the mechanisms of ascending and descending pain pathways. Although the general mechanisms and circuits are well known, less is known about the micro-circuitry, cell types, receptor distribution and receptor signaling mechanisms within these pain pathways. Our lab has identified a novel regulator of MOR signaling, phosphatidylethanolamine-binding protein (PEBP), and characterized its role in MOR signaling and MOR mediated behavior. PEBP in its unphosphorylated monomeric form binds and inhibits Raf-1, and when phosphorylated by PKC it will dimerize, bind, and inhibit GRK2. We hypothesized that inhibiting PEBP will increase free GRK2 and thus βarrestin2 recruitment to the MOR and decrease morphine-induced antinociception. Indeed, inhibition of PEBP with an inhibitor, locostatin, reduced βarrestin2 recruitment *in vitro*. Conversely, activating PKC resulted in phosphorylation of PEBP and a subsequent decrease in βarrestin2 recruitment. Moreover, inhibiting PEBP in the spinal cord with locostatin or using CRISPR resulted in substantial decreases (>50%) in morphine-induced antinociception via the tail flick assay. We next sought to investigate the specific physiological role of PEBP in regulating endogenous antinociception. To do this we injected locostatin intrathecally (*it*) and then injected DAMGO intracerebroventricularly (*icv*) to activate OFF-cells, promoting descending endogenous opioid release in the spinal cord. We then performed [^{35}S]-GTPγS coupling for MOR on these spinal cords and found *icv* DAMGO treatment alone caused a 29% decrease in [^{35}S]-GTPγS coupling; *it*locostatin treatment alone caused a 34% decrease; The combination of *it* locostatin followed by *icv* DAMGO resulted in a 73% decrease. These

results suggest a gating mechanism whereby incoming nociceptive information sensitizes the MOR through a PEBP-dependent regulation, thus promoting endogenous opioid antinociception from descending inputs.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.15/J10

Topic: D.03. Somatosensation – Pain

Support: University of Toronto Centre for the Study of Pain
Canadian Pain Society

Title: The neural basis of opioid-mediated conditioned analgesia in chronic neuropathic pain

Authors: *C. CHO, V. MICHAILIDIS, A. FATIMA, H. PARK, B. PRESSWALA, N. DZIEKONSKI, A. LEONETTI, L. J. MARTIN;
Univ. of Toronto, Mississauga, ON, Canada

Abstract: Objective: Chronic pain can be interpreted as a maladaptive pain memory that is susceptible to alterations through learning such as conditioning. In support, conditioned analgesia represents a phenomenon where an inert treatment induces pain relief. The objective of the study was to identify the neural pathways of the central nervous system responsible for conditioned analgesia using a mouse model of chronic neuropathic pain.
Methods: Mechanical pain thresholds were measured in 6-8wk old male CD-1 mice, before and following spared nerve injury (SNI). The SNI mice then underwent a four-day conditioning phase where contextual and tactile stimuli were coupled with an unconditioned drug stimulus (morphine, 10mg/kg). Following the conditioning period, the SNI mice were administered either saline or an opioid receptor antagonist. Following behavioural testing, neuronal activity was mapped in the spinal cord and brain by probing for c-fos expression using immunoblotting and immunohistochemistry.
Results: Saline administration following pharmacological conditioning induced analgesia comparable to that of morphine, which was reversed by naloxone. Systemic administration of antagonists for opioid receptor subtypes mu, delta and kappa demonstrated that inhibition of mu-opioid receptor (MOR), but not delta- or kappa-opioid receptors, blocked saline-induced analgesia, suggesting that opioid-mediated placebo analgesia occurs via MOR. Immunoblotting and immunohistochemical analyses revealed significant changes in c-fos expression in the spinal cord and the pain processing regions of the brain.
Conclusions: We demonstrate a novel animal model of conditioned analgesia within the context

of chronic neuropathic pain. This is accompanied by corresponding changes of neuronal activities in the central nervous system similar to those observed in humans, warranting further investigations in order to elucidate the underlying neural basis for conditioned analgesia.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.16/J11

Topic: D.03. Somatosensation – Pain

Support: NIDA Grant DA042565

Title: Local administration of a CB1 antagonist reveals endocannabinoid tone regulating pain-modulating neurons in the rostral ventromedial medulla

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Abstract: Systemic administration of cannabinoids produces analgesia that is mediated in part through brainstem pain modulating systems. These systems have a major output through the rostral ventromedial medulla (RVM). Blocking cannabinoid receptor 1 (CB1) in the RVM suppresses analgesia produced by CB agonists or stress. *In vitro* studies have shown that blocking presynaptic CB1 receptors in RVM disinhibits GABA release, suggesting a local endocannabinoid tone. However, how this endocannabinoid tone influences the pain-modulating circuitry within the RVM *in vivo*, and implications of this tone for pain processing remain to be determined. The aim of these experiments was to test the hypothesis that endocannabinoid tone in the RVM modulates activity of distinct classes of pain modulating neurons: pro-nociceptive ON- and anti-nociceptive OFF-cells. Activity of identified ON- and OFF-cells and heat-evoked paw withdrawal were recorded in lightly anesthetized male and female Sprague-Dawley rats. Microinjection of a CB1 receptor antagonist, SR141716 (200 pmol/200 nL), in the RVM unexpectedly increased the ongoing firing of ON-cells, while vehicle injection did not change neuronal activity. Activity of OFF-cells was unchanged. NEUTRAL-cells, RVM neurons without a known role in pain modulation, also showed no change in activity following CB1 receptor block. These data indicate that, at least under basal conditions, endocannabinoid action in RVM limits activity of pro-nociceptive ON-cells, and thus provides an ongoing restraint of nociceptive transmission.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

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Program #/Poster #: 482.17/J12

Topic: D.03. Somatosensation – Pain

Support: NINDS R01NS106953
NINDS F31NS103472

Title: Functional and anatomical characterization of descending periaqueductal gray (PAG) projections and their role in pain modulation

Authors: *J. G. GRAJALES-REYES[1], V. K. SAMINENI[1], A. LEGARIA[1], C. E. PEDERSEN[2], M. R. BRUCHAS[2], R. W. GEREAU, IV[1];
[1]Anesthesiol., Washington Univ. Sch. of Med., St Louis, MO; [2]Dept. of Anesthesiol. and Pain Med., Univ. of Washington, Seattle, WA

Abstract: Endogenous analgesic pathways embody an alternative target for the development for chronic pain therapies. Previous studies have demonstrated the role of the ventrolateral periaqueductal gray (vlPAG) in descending pain modulation. It has been proposed that tonic GABAergic neurotransmission at the level of the vlPAG serves to inhibit efferent excitatory projections that mediate descending analgesia. Disinhibition of these projection neurons allows subsequent activation of rostral ventromedial medulla (RVM) neurons that inhibit nociception at the level of the spinal cord. However, lack of cell-type specificity in these studies has prevented the determination of the role of specific subsets of vlPAG neurons in analgesia. We have utilized recently developed genetic tools to selectively manipulate and monitor the activity of subclasses of vlPAG neurons to identify the circuit components critical for analgesia. Our data suggest that increasing the activity of glutamatergic vlPAG neurons or decreasing the activity of GABAergic vlPAG neurons results in increases in sensory thresholds in uninjured animals, while ameliorating hyperalgesia associated with chronic pain states. We hypothesized that efferent projections to the RVM from the vlPAG are partially responsible for the observed analgesia in our previous study. Population-specific anatomical tracing revealed that the nearly all neurons projecting from vlPAG to the RVM (nucleus raphe magnus) are glutamatergic. Optogenetic stimulation of these vlPAG-RVM neurons results in elevation of thermal thresholds in uninjured animals and reverses thermal hyperalgesia associated with inflammatory states. Our results provide direct experimental evidence supporting the GABA disinhibition hypothesis, highlighting the role of descending glutamatergic neurotransmission at the level of the PAG-RVM as a key component of endogenous analgesic pathways. This work is supported by funds from NINDS: R01NS106953 to RG and F31NS103472 to JGGR.

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Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.18/J13

Topic: D.03. Somatosensation – Pain

Title: Transcranial direct-current stimulation over the primary motor cortex reduces A-fibre mediated mechanical sensitivity in a severe area of capsaicin-induced secondary hyperalgesia

Authors: *S. HUGHES, G. WARD, P. H. STRUTTON;
Imperial Col. London, London, United Kingdom

Abstract: Transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) has shown promise as a novel analgesic therapy for chronic pain patients. However, the top-down analgesic mechanisms at the spinal level remain unknown. This study therefore used the capsaicin model of ongoing pain in healthy volunteers to investigate the top-down effects of M1-tDCS on spinal cord measures of central sensitisation (i.e. secondary hyperalgesia). Using a within-subject design, 13 subjects were recruited and underwent baseline electrical pain perception (EPP) threshold and mechanical stimulus response (S/R) function testing before topical application of 1% capsaicin cream over the L5 dermatome. Ongoing pain ratings were assessed using visual analogue scale (VAS) ratings. EPP thresholds were used to determine severe and mild areas of secondary hyperalgesia by measuring the degree of change in pain threshold at 4 points within an area covering 98.9 cm2 around the neurogenic flare response (severe: 62.21 ± 4.70% of baseline versus mild: 93.45 ± 6.97% of baseline; $p<0.0001$). Mechanical S/R function was then re-assessed in the severe area of secondary hyperalgesia. ANOVA revealed an effect of mechanical stimulus ($F = 19.57$; $p<0.001$) and time (pre and post-capsaicin, $F = 9.87$; $p<0.01$) resulting in a leftward shift of the S/R curve. The analgesic effects of tDCS over M1 (20 mins anodal, 2mA) or sham stimulation were then investigated in a randomised, double-blind manner. tDCS reduced ongoing VAS ratings (post-tDCS: 43.18 ± 5.15 versus post-sham: 52.32 ± 3.57; $p < 0.05$), increased EPP thresholds (post-tDCS: 82.8 ± 12.7% of baseline; $p < 0.01$) and caused a rightward shift in the mechanical S/R curve, which was not evident in the sham condition. There was a significant correlation between the tDCS-induced change in EPP threshold and change in mechanical sensitivity in the area of secondary hyperalgesia ($r2 = 0.45$; $p<0.01$). These data demonstrate that EPP can be used to map mild and severe areas of secondary hyperalgesia and that M1-tDCS can modulate the severity of secondary hyperalgesia.

Disclosures: **S. Hughes:** None. **G. Ward:** None. **P.H. Strutton:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

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Program #/Poster #: 482.19/J14

Topic: D.03. Somatosensation – Pain

Title: Changes in the balance of pro-versus anti-nociception during the development of capsaicin-induced secondary hyperalgesia in healthy volunteers

Authors: *Y. RHO, A. REDDY, S. HUGHES, P. STRUTTON;
Imperial Col. London, London, United Kingdom

Abstract: Changes in the levels of spinal cord facilitation and inhibition are fundamental mechanisms associated with the development of chronic pain. However, it is currently unknown whether similar changes occur during the development of experimentally-induced ongoing pain and secondary hyperalgesia in human pain models. In this study, we explored temporal changes in the balance of pro- (i.e. facilitation) and anti- (i.e. inhibition) nociception using well validated psychophysical measures of spinal cord excitability and endogenous inhibitory pathways. Twenty-four healthy subjects were recruited and underwent baseline conditioned pain modulation (CPM), wind up and electrical pain perception (EPP) threshold testing before application of 1% topical capsaicin cream over an area of the L5 dermatome. Responders to capsaicin (n=13) had their EPP thresholds and wind up ratios re-measured at time points during the development and following the onset of secondary hyperalgesia. CPM was measured again at the end of the study protocol. Capsaicin caused a gradual decrease in EPP thresholds (pre-capsaicin: 8.30 ± 0.73 mA; early development: 7.83 ± 0.95 mA; late development: 7.17 ± 0.96 mA; post-capsaicin: 6.88 ± 0.78 mA; $p<0.01$) within a 98.9 cm2 area surrounding the neurogenic flare response and an increase in wind up ratio (pre-capsaicin: 2.86±0.39; early development: 2.77 ± 0.35; late development: 3.44 ± 0.51; post-capsaicin: 3.74 ± 0.44; $p<0.01$) during the development and onset of secondary hyperalgesia. There was also a change in CPM following the onset of secondary hyperalgesia (pre-capsaicin: 19.00 ± 3.48%; post-capsaicin: 1.98 ± 4.23%; $p<0.01$). Non-responders to capsaicin (n = 11) showed no changes in either CPM or windup. These data suggest that the changes observed in the responders to capsaicin are mediated by a gradual shift in the balance of pro- versus anti-nociception during the development of secondary hyperalgesia. It may be possible to reduce the severity of capsaicin-induced pain sensitivity by modulating the balance of endogenous pro- versus anti-nociceptive drive.

Disclosures: Y. Rho: None. **A. Reddy:** None. **S. Hughes:** None. **P. Strutton:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.20/J15

Topic: D.03. Somatosensation – Pain

Title: Attenuation of capsaicin-induced ongoing pain and secondary hyperalgesia by virtual reality stimulation is related to the activity within endogenous pain inhibitory pathways

Authors: S. HUGHES, H. ZHAO, E. AUVINET, ***P. H. STRUTTON**;
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Abstract: Virtual reality (VR) interventions have shown promise as a novel distraction-based analgesic therapy for use in painful medical procedures and during acute pain states. There is now a growing body of evidence that suggests VR can be used in the management of chronic pain. However, there has been limited investigation into the analgesic mechanisms associated with VR and whether it can modulate the altered nociceptive processing associated with chronic pain. We examined the relationship between psychophysical measures of endogenous analgesia and the effects of VR on capsaicin-induced ongoing pain perception and secondary hyperalgesia in healthy volunteers. Nineteen subjects had baseline conditioned pain modulation (CPM) and electrical pain perception (EPP) thresholds measured prior to the application of 1% topical capsaicin cream over the L5 dermatome. Visual analogue scale (VAS) ratings were measured to track the development of an ongoing pain state and changes in EPP thresholds outside of the neurogenic flare indicated the presence of secondary hyperalgesia. Responders to capsaicin (n=15) had analgesic effects measured during and after a randomised 10-minute exposure to either real or sham (i.e. 2D computer monitor screen) VR stimulation. VR was associated with a reduction in ongoing pain ratings (mean±SEM post capsaicin VAS: 62.17 ± 2.07 versus during VR VAS: 47.67 ± 2.94; $p<0.001$) and an increase in EPP threshold (post capsaicin EPP threshold: 5.33 ± 0.47 mA versus during VR EPP threshold: 6.78 ± 0.54 mA; $p<0.0001$) which both returned to a sensitised level following removal of the VR headset. CPM showed a significant correlation with changes in secondary hyperalgesia ($r2 = 0.68$, $p<0.001$), but not with changes in ongoing pain perception ($r2 = 0.063$, $p > 0.05$). These results indicate that VR stimulation may be a promising new behavioural and analgesic therapy for use in chronic pain patients. We demonstrate that the analgesic effects are mediated through two distinct endogenous analgesic pathways; one of which is CPM-dependent and likely involves the interaction between cortical regions mediating top-down modulation of descending inhibitory pathways and the other is CPM-independent and is likely to be mediated through cortical areas involved in distraction.

Disclosures: P.H. Strutton: None. **S. Hughes:** None. **H. Zhao:** None. **E. Auvinet:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.21/J16

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS038261
NIH Grant NS081121
NIH Grant NS106902

Title: Correlation between pain-related behaviors and synaptic transmission in amygdala CRF neurons in a neuropathic pain model

Authors: *T. KIRITOSHI[1], V. A. YAKHNITSA[1], V. NEUGEBAUER[1,2,3];
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., [3]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The amygdala is an important contributor to pain-related emotional-affective conditions and pain modulation. The central nucleus of amygdala (CeA) serves as a major output nucleus of the amygdala. CeA activity is increased and mechanistically linked to pain-related behaviors in different pain conditions. Evidence suggests that a subset of CeA neurons containing corticotropin releasing factor (CRF) is critically involved in the modulation of pain and affective disorders. Here we used optogenetic activation or silencing of CRF-CeA neurons to determine their contribution to pain related behaviors. Elevated plus maze test performance and vocalizations evoked by innocuous and noxious stimuli of the hind paw were measured in adult neuropathic rats (4-6 weeks after spinal nerve ligation, SNL) and control rats. For optogenetic activation or silencing of CRF neurons, a Cre-inducible viral vector (DIO-AAV) encoding channel rhodopsin 2 (ChR2) or enhanced Natronomonas pharaonis halorhodopsin (eNpHR3.0) was injected stereotaxically into the right CeA of transgenic Crh-Cre rats, kindly made available to us by Dr. Robert Messing's group, UT Austin. Animals were allowed to recover for channel expression. For wireless optical stimulation of ChR2 or eNpHR3.0 expressing CRF-CeA neurons, an LED optic fiber was stereotaxically implanted into the right CeA in control and neuropathic rats. Optical activation of CRF-CeA neurons increased the vocalizations under normal condition, whereas optical silencing of CRF-CeA neurons decreased vocalizations and ameliorated anxiety like behaviors in the neuropathic pain model. Subsequent patch-clamp recordings in brain slices confirmed that functional ChR2 and eNpHR3.0 were expressed in CRF-CeA neurons. No response to light stimulation was observed in CRF-negative CeA neurons. The data provide evidence for an important contribution of CRF-CeA neurons to neuropathic pain-related behaviors and for their ability to generate pain behaviors in the absence of injury under control condition.

Disclosures: **T. Kiritoshi:** None. **V. Neugebauer:** None. **V.A. Yakhnitsa:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.22/J17

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS038261
NIH Grant NS081121
NIH Grant NS106902

Title: Optogenetic stimulation of amygdala CRF neurons modulates pain-related behaviors in a rodent model of neuropathic pain

Authors: *V. NEUGEBAUER[1,2,3], M. MAZZITELLI[1], V. A. YAKHNITSA[1];
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., [3]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The amygdala is an important contributor to pain-related emotional-affective conditions and pain modulation. The central nucleus of amygdala (CeA) serves as a major output nucleus of the amygdala. CeA activity is increased and mechanistically linked to pain-related behaviors in different pain conditions. Evidence suggests that a subset of CeA neurons containing corticotropin releasing factor (CRF) is critically involved in the modulation of pain and affective disorders. Here we used optogenetic activation or silencing of CRF-CeA neurons to determine their contribution to pain related behaviors. Elevated plus maze test performance and vocalizations evoked by innocuous and noxious stimuli of the hind paw were measured in adult neuropathic rats (4-6 weeks after spinal nerve ligation, SNL) and control rats. For optogenetic activation or silencing of CRF neurons, a Cre-inducible viral vector (DIO-AAV) encoding channel rhodopsin 2 (ChR2) or enhanced Natronomonas pharaonis halorhodopsin (eNpHR3.0) was injected stereotaxically into the right CeA of transgenic Crh-Cre rats, kindly made available to us by Dr. Robert Messing's group, UT Austin. Animals were allowed to recover for channel expression. For wireless optical stimulation of ChR2 or eNpHR3.0 expressing CRF-CeA neurons, an LED optic fiber was stereotaxically implanted into the right CeA in control and neuropathic rats. Optical activation of CRF-CeA neurons increased the vocalizations under normal condition, whereas optical silencing of CRF-CeA neurons decreased vocalizations and ameliorated anxiety like behaviors in the neuropathic pain model. Subsequent patch-clamp recordings in brain slices confirmed that functional ChR2 and eNpHR3.0 were expressed in CRF-CeA neurons. No response to light stimulation was observed in CRF-negative CeA neurons. The data provide evidence for an important contribution of CRF-CeA neurons to

neuropathic pain-related behaviors and for their ability to generate pain behaviors in the absence of injury under control condition.

Disclosures: V. Neugebauer: None. **M. Mazzitelli:** None. **V.A. Yakhnitsa:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.23/J18

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS106902
NIH Grant NS038261

Title: Kappa opioid receptor blockade restores inhibition of amygdala CRF neurons in a functional pain model

Authors: *M. HEIN[1], G. JI[1,2], E. NAVRATILOVA[4], F. PORRECA[4], V. NEUGEBAUER[1,2,3]; [1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., [3]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [4]Pharmacol., Univ. of Arizona Col. of Med., Tucson, AZ

Abstract: Neuroplastic changes in the central nervous system have been implicated not only in pain conditions associated with an identifiable injury, but also in functional pain syndrome (FPS), in which the pain cannot be attributed to tissue pathology. Mechanisms of FPS remain to be determined, but these conditions are typically triggered by stress, which can create a chronic pain condition. Corticotropin releasing factor (CRF) and its CRF1 receptor in the amygdala have been linked to emotional-affective behaviors and pain modulation. The amygdala is also a major site of opioid receptors. The central nucleus of the amygdala (CeA), in particular, serves as a major site of amygdala output, and exhibits high levels of expression of the Gi/o-coupled kappa opioid receptor (KOR). KOR activation by its endogenous ligand, dynorphin, or agonists can have adverse effects and oppose mu-opioid receptor-mediated actions. Here we tested the hypothesis that blockade of KOR signaling restores inhibitory control of CRF neurons in the central nucleus (CeA) in a rat model of FPS. Brain slice electrophysiology was used to determine the effects of a KOR antagonist (Nor-Binaltorphimine, nor-BNI) on CRF-CeA neurons. These neurons can be visualized in brain slices from transgenic Crf-Cre rats, kindly made available to us by Dr. Robert Messing's group, UT Austin. AAV5-ChR2-CaMKII-eYFP was injected into the lateral parabrachial area (LPB) to allow optical activation of glutamatergic synaptic input to CeA neurons. The FPS model was induced by morphine priming for 7 days (using subcutaneously implanted mini osmotic pumps) followed 4 weeks later by one hour of restraint stress on two consecutive days. The control group received morphine without stress. Whole-cell

patch-clamp recordings of CRF-CeA neurons found that in the FPS model, nor-BNI increased LPB-evoked glutamate-driven inhibitory synaptic currents (IPSCs, feedforward inhibition) as well as spontaneous and miniature IPSC frequency, but not amplitude, while decreasing neuronal excitability (frequency-current F-I relationship). The data suggest that blockade of KOR signaling in a rodent model of FPS restores synaptic inhibition of CRF-CeA neurons through a presynaptic mechanism of action.

Disclosures: **M. Hein:** None. **G. Ji:** None. **E. Navratilova:** None. **F. Porreca:** None. **V. Neugebauer:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.24/J19

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS106902
NIH Grant NS038261

Title: Kappa opioid receptors mediate hyperactivity of central amygdala neurons in a functional pain model

Authors: ***G. JI**[1,2], E. NAVRATILOVA[4], F. PORRECA[4], V. NEUGEBAUER[1,2,3];
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., [3]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [4]Pharmacol., Univ. of Arizona Col. of Med., Tucson, AZ

Abstract: The dynorphin/KOR system has emerged as a novel target for the treatment of stress-related mood disorders including anxiety, depression, drug seeking and relapse. KOR is widely, but specifically, expressed in both rodent and human brain neuronal circuits including the amygdala. The amygdala is part of the limbic brain and plays an important role in mediating emotional responses to pain as well as fear, anxiety and stress. The central nucleus of the amygdala (CeA) is an important output structure that may sustain chronic pain through descending pain facilitatory outputs to brain/brainstem areas for behavioral modulation. Our previous studies showed that stress-induced activation of KOR promotes sensory and affective pain behaviors, and blockade of KOP signaling in the right CeA blocks stress-induced pain responses, suggesting enhanced descending facilitation from the amygdala as a mechanism to amplify nociceptive input following stress. In this study, systems electrophysiology was used to determine the effects of stress-induced activation of KOR signaling on CeA neurons. Extracellular single-unit recordings were made from CeA neurons in anesthetized adult rats that were morphine-primed and exposed to restraint stress (functional pain model) compared to

controls. Background activity and evoked responses to brief (15 s) test stimuli (compression of the hindpaw) were measured. Background activity and evoked responses of CeA neurons were increased in morphine-primed, stressed rats compared to controls. Administration of a KOR agonist (U-69593) by microdialysis into the CeA increased the responses of CeA neurons to noxious and innocuous stimuli in control rats, but not in the functional pain model. Administration of a KOR antagonist (nor-BNI) by microdialysis into the CeA reduced the responses of CeA neurons to noxious and innocuous stimuli in morphine-primed, stressed rats, but not in control rats. The data suggest that KOR signaling mediates activation of CeA neurons in stress-related functional pain conditions.

Disclosures: G. Ji: None. **E. Navratilova:** None. **F. Porreca:** None. **V. Neugebauer:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.25/J20

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS038261
NIH Grant NS081121

Title: Group II metabotropic glutamate receptors modulate synaptic transmission in CRF-CeA neurons in an arthritic pain model

Authors: *M. MAZZITELLI[1], V. NEUGEBAUER[1,2,3];
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., [3]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The amygdala plays an important role in the regulation of emotional-affective components of pain and in pain modulation. The central nucleus of amygdala (CeA) serves major output functions. The CeA receives nociceptive information via the external lateral parabrachial nucleus (PB). The CeA is also the main source for extra-hypothalamic corticotropin releasing factor (CRF), which is involved in several neuropsychiatric disorders. CRF-CeA containing neurons project to other brain regions involved in behaviors and pain. Gi/o-coupled group II metabotropic glutamate receptors (mGluR2 and mGluR3) are expressed in different brain regions, including the amygdala. Their activation can decrease neurotransmitter release and regulate synaptic plasticity, but effects of the modulation of group II mGluRs and subtypes on CRF-CeA neurons remains to be determined. In this study we address this question in a rodent model of arthritic pain. Brain slice physiology was performed to determine the effects of a group II mGluR agonist (LY379268 disodium salt) and a positive allosteric modulator (PAM) selective for mGluR2 (LY487379 hydrochloride) on CRF-CeA neurons from normal rats and arthritic rats

(5-6 h postinduction of a kaolin/carrageenan-monoarthritis in the left knee joint). In order to visualize CRF-CeA neuron in brain slices, we used transgenic Crh-Cre rats, kindly made available to us by Dr. Robert Messing's group, UT Austin. Whole-cell patch-clamp recordings were used to investigate monosynaptic excitatory postsynaptic currents (EPSCs) and glutamate driven inhibitory postsynaptic currents (IPSCs) evoked from PB inputs. Activation of group II mGluRs by LY379268 resulted in a reduction of EPSCs and IPSCs in the arthritic condition. Similarly, selective activation of mGluR2 by LY487379 decreased the synaptic responses evoked by PB stimulation. These results suggest that group II mGluRs, and particularly mGluR2, in the amygdala can regulate synaptic transmission of CRF neurons, which could explain the anxiolytic and antinociceptive properties of pharmacological agents acting on group II mGluRs.

Disclosures: M. Mazzitelli: None. **V. Neugebauer:** None.

Poster

482. Somatosensation: Descending Modulation of Pain

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 482.26/J21

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS038261
NIH Grant NS081121
NIH Grant NS106902

Title: Phenotypic differences in potassium (SK) channel dysfunction in the amygdala in a rat model of neuropathic pain

Authors: *V. A. YAKHNITSA[1], T. KIRITOSHI[1], V. NEUGEBAUER[1,2,3];
[1]Pharmacol. and Neurosci., [2]Ctr. of Excellence for Translational Neurosci. and Therapeut., [3]Garrison Inst. on Aging, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: The amygdala is an important limbic structure for the emotional-affective dimension of pain. Small-conductance calcium-activated potassium (SK) channels are expressed in the central amygdala (CeA) and inhibit neuronal excitability under normal conditions. We discovered dysfunction of SK-channels in neuropathic pain conditions that contributes to increased CeA neuronal activity and pain behaviors. Here we tested the hypothesis that the magnitude of neuropathic pain behaviors predicts and correlates with the amount of SK-channel dysfunction in CeA. Mechanical sensitivity (von Frey test) and audible (nocifensive response) and ultrasonic (affective response) vocalizations were measured in neuropathic rats (L5 spinal nerve ligation model, SNL) and in sham controls 4 weeks after surgery. Anxiety-like behaviors were evaluated using the open field and elevated plus maze tests, and depression-like behaviors were measured on the forced swimming and sucrose preference tests. SNL rats showed reduced

withdrawal thresholds and increased vocalizations compared to sham controls. Anxiety-like behaviors occurred in 58% while depression-like behaviors were observed in 30% of SNL rats. Comorbidity of anxiety and depression was found in 18% of rats. Patch-clamp recordings of regular firing lateral CeA neurons in brain slices from SNL rats with anxiety/depression comorbidity found reduced mAHP, increased action potential frequency-current (F-I) relationship, and enhanced excitatory synaptic transmission compared to sham controls and to the SNL phenotype with low anxiety and without depression-like behavior. The data suggest close interaction between amygdala plasticity and neuropathic pain. SK channel dysfunction contributes to maladaptive neuropathic pain-related amygdala plasticity that correlates with anxiety- and depression-like behaviors.

Disclosures: V.A. Yakhnitsa: None. **T. Kiritoshi:** None. **V. Neugebauer:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.01/J22

Topic: D.03. Somatosensation – Pain

Support: Indiana Spinal Cord and Brain Injury Research Grant 2017
Showalter Research Grant 2016

Title: Columbianadin reduces oxaliplatin-induced neuropathic pain through an inhibition of L-type voltage-gated calcium currents in dorsal root ganglion neurons

Authors: *X. SU[1,2], B. WU[1,3], W. ZHANG[1], Y.-H. JI[3], Q. WANG[2,4], *Z.-Y. TAN[1];
[1]Indiana Univ., Indianapolis, IN; [2]Heilongjiang Univ. of Chinese Med., Harbin, China;
[3]Shanghai Univ., Shanghai, China; [4]Guangdong Pharmaceut. Univ., Guangzhou, China

Abstract: *Radix angelicae pubescentis* (RAP) has been used in Chinese traditional medicine to treat painful diseases such as rheumatism and headache for centuries. A previous study has reported that columbianadin (CBN), a major coumarin in RAP inhibits acute and inflammatory pain behaviors. However, the effects of CBN on neuropathic pain behaviors have not been reported. Moreover, it has not been reported what might be the potential mechanism underlying the anti-nociceptive effects of CBN, nor if CBN modulates any ion channels. In the present study, we studied the effects of CBN, compared to another major coumarin of RAP osthole (OST), on nociceptive behaviors in a neuropathic pain model of mouse induced by a chemotherapy drug oxaliplatin. We also studied the effects of CBN, compared to OST, on voltage-gated calcium and sodium currents in small dorsal root ganglion (DRG) neurons of mice. We found that CBN largely inhibited both mechanical and cold hypersensitivity induced by oxaliplatin while OST largely inhibited the mechanical hypersensitivity. Using whole-cell patch

clamp recordings, we further found that both CBN and OST significantly inhibited calcium currents (*Ica*), but not sodium currents in small-sized DRG neurons. However, CBN displayed a stronger inhibitory effect on *Ica* compared to OST. Moreover, our data suggested that CBN selectively inhibits the L-type *Ica* while OST inhibits all types of *Ica* non-selectively. These results suggest that CBN inhibits neuropathic pain behaviors through an inhibition of L-type calcium currents in nociceptive DRG neurons. In addition, the inhibition of different types of calcium currents in DRG neurons might contribute to the different pattern of anti-nociceptive effects of coumarins.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.02/J23

Topic: D.03. Somatosensation – Pain

Support: R01NS065926

Title: Optimizing pharmacological targeting of AMPK for treatment of paclitaxel-induced peripheral neuropathy

Authors: *K. E. INYANG[1], T. MCDOUGAL[2], E. RAMIREZ[1], M. WILLIAMS[1], A. KAVELAARS[4], C. J. HEIJNEN[6], G. O. LAUMET[5], M. D. BURTON[3], G. O. DUSSOR[3], T. J. PRICE[7];
[2]Neurosci., [3]Behavioral and Brain Sci., [1]Univ. of Texas At Dallas, Richardson, TX; [4]Neuroimmunology Lab., [5]Univ. of Texas MD Anderson Cancer Ctr., Houston, TX; [6]Lab. for Neuroimmunology, Univ. of Texas M D Anderson Cancer Ctr., Houston, TX; [7]Sch. of Behavioral and Brain Sci., UTD, Richardson, TX

Abstract: Chronic pain is more prominent in women than in men, yet until relatively recently most preclinical pain research was done almost exclusively in male animals. Recent studies have shown profound sex differences in mechanisms of chronic pain. Many of these findings have been in the chemotherapy-induced neuropathic pain (CIPN) area. We tested the hypothesis that AMPK activators could be effective in reversing established CIPN in male and female mice. The indirect AMPK activator metformin has been previously shown by our lab to cause a reversal of neuropathic pain induced by spared nerve injury (SNI), but only in male mice. However, metformin is effective in preventing, but not reversing, CIPN in female mice. These discrepant findings suggest a complex interaction of metformin and sex-specific anti-neuropathic pain effects. We sought to gain more clarity around this issue by using different classes of AMPK

activators in a common CIPN model in mice. Therefore, we used structurally distinct AMPK activators narciclasine (NCLS) and MK 8722 to treat paclitaxel-induced mechanic hypersensitivity and hyperalgesic priming in male and female mice. Efficacy of these compounds to both prevent and reverse hypersensitivity were tested by giving the drug treatment concurrently and following paclitaxel respectively. Paclitaxel (4 mg/kg) was given every other day for a week while AMPK activators were given every day for 7 consecutive days. We found that indirect AMPK activator NCLS (3 mg/kg) was able to prevent and reverse mechanical hypersensitivity as well as block hyperalgesic priming in male and female mice while the direct AMPK activator MK-8722 (30 mg/kg) only blocked priming. We interpret our findings as evidence that indirect AMPK activators are more effective for treating pain hypersensitivity in paclitaxel-induced neuropathy and that both direct and indirect AMPK activators can be effective in male and female mice. These findings have important implications for the development of AMPK-targeting therapeutics for pain treatment.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.03/J24

Topic: D.03. Somatosensation – Pain

Title: Investigation of the plasma cytokine/chemokine profile of the chronic constriction injury rat model of neuropathic pain: Relevance to pharmacological reversal of allodynia

Authors: *E. SOKOLOWSKA[1], J. PRENDERVILLE[1], M. BIANCHI[1], A. THOMAS[2], A. FISHER[2], N. UPTON[2];
[1]Transpharmation Ireland Ltd, Dublin, Ireland; [2]Transpharmation Ltd., London, United Kingdom

Abstract: Neuropathic pain (NeuP) describes a heterogeneous group of chronic pain disorders arising from lesion or disease of the somatosensory system. Gabapentin (GBP) and pregabalin (PGB) are among the first line treatments, however, both are associated with poor efficacy and undesirable side-effects. Identifying a plasma biomarker to track disease progression or predict pharmacological efficacy will facilitate drug discovery in NeuP. We have used the chronic constriction injury (CCI) model to investigate plasma cytokine/chemokine profile after NeuP induction and following GBP and PGB treatment. The CCI model was induced in male Sprague-Dawley rats (n=16) by unilateral ligation of the sciatic nerve. Paw withdrawal threshold (PWT; mechanical allodynia) was assessed using von-Frey hairs. PWT was measured at baseline (day 0), day 20 following nerve ligation, 2h (day 27) post-GBP (100mg/kg, PO) and, 2h and 24h (day

42/43) post-PGB (30mg/kg, PO). Plasma IFN-γ, IL-1β, IL-4, IL-5, IL-6, KC/GRO, IL-10, IL-13 TNF-α were analysed at these time points. CCI resulted in increased mechanical sensitivity as measured by PWT. This was reversed by both GBP and PGB at the 2h time point only. Plasma IL-5 was increased following CCI and this was reversed by GBP treatment only. IL-13 was unaffected by CCI and was increased 2h following PGB treatment. TNF-α was decreased by CCI and further decreased by PGB only, at both time points. CCI had no effect on IL-6 and IL-10, both drugs increased these targets. KC/GRO was unaffected by CCI but decreased by GBP and PGB. This study demonstrates the acute efficacy of both GBP and PGB in the rat CCI model of NeuP. Reversal of increased plasma IL-5 following CCI induction was specific to GBP treatment only. IL-13, a cytokine associated with suppression of NeuP, was acutely increased by PGB consistent with its efficacy. The plasma cytokine/chemokine profile here suggests a complex interaction between NeuP disease progression, pharmacological intervention and inflammatory signalling. This study has identified potential plasma markers of NeuP progression and treatment efficacy. Future studies will be designed to further explore the translational potential of these inflammatory markers.

Disclosures: **E. Sokolowska:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **J. Prenderville:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **M. Bianchi:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **A. Thomas:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **A. Fisher:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **N. Upton:** A. Employment/Salary (full or part-time):; Transpharmation Ltd..

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.04/J25

Topic: D.03. Somatosensation – Pain

Support: Partially supported by Conacyt, grants CB-2012/179294 (to VG-S) and PN-5098 (to RD-L).

Title: Sex-dependent antiallodynic effect of α_5GABA$_A$ receptors and differences in α_5GABA$_A$ receptors regulation in neuropathic rodents

Authors: *Ú. FRANCO-ENZÁSTIGA[1], A. B. SALINAS-ABARCA[1], R. GONZÁLEZ-BARRIOS[3], B. SÁNCHEZ-HERNÁNDEZ[4], P. BARRAGAN-IGLESIAS[5], G. GARCÍA[2], J. MURBARTIAN[2], T. J. PRICE[5], R. DELGADO-LEZAMA[6], V. GRANADOS-SOTO[1]; [1]Neurobio. of Pain laboratory, Dept. de Farmacobiología, [2]Dept. de Farmacobiología, Cinvestav, Sede Sur, Mexico City, Mexico; [3]Cancer Biomed. Res. Unit, Inst. Nacional de Cancerología (INCan), Mexico City, Mexico; [4]Dept. de Genética, Inst. Nacional de Ciencias Médicas y

Nutrición Salvador Zubirán, Mexico City, Mexico; [5]Sch. of Behavioral and Brain Sci., UTD, Richardson, TX; [6]Dept. de Fisiología, Biofísica y Neurociencias, Cinvestav, IPN, Mexico City, Mexico

Abstract: It has been shown that the gene *GABRA5* coding for the extrasynaptic α_5 subunit-containing $GABA_A$ (α_5GABA_A) receptors is expressed at higher levels in striatum of women. Moreover, positive allosteric modulators selective for α_5GABA_A receptors reduce stress only in female mice. These data suggest sex differences in the regulation and/or function of α_5GABA_A receptors in the nervous system. It is currently known that α_5GABA_A receptors are expressed in dorsal root ganglia (DRG) and spinal cord (SC) participating in chronic pain. The aim of this study was to investigate whether α_5GABA_A receptors actions are sex-dependent in neuropathic rats and mice. We also evaluated the role of estrogen on the action of α_5GABA_A receptors in neuropathic rats. Moreover, we examined the changes in protein and mRNA levels of α_5GABA_A receptors in DRG and SC of neuropathic animals. Finally, we investigated the influence of epigenetics on the profiles of *Gabra5* expression by analyzing DNA methylation levels in *Gabra5* CpG island in DRG from female and male neuropathic rats. L-655,708, α_5GABA_A receptors inverse agonist (0.15-15 nmol, i.t.), produced an antiallodynic effect in neuropathic female rats and mice. However, L-655,708 elicited a lower effect in male animals. Ovariectomy abrogated the antiallodynic effect of L-655,708 in neuropathic female rats, while 17β-estradiol (14 days, 20 µg/kg, s.c.) restored it. The recovered effect of L-655,708 by 17β-estradiol was lost in rats injected with the specific antagonist of estrogen receptor ICI 182,780 (3 days, 50 µg/kg, i.t.). Nerve injury increased α_5GABA_A receptors protein and mRNA in DRG and SC in female rats and mice and decrease it in males. Moreover, nerve injury increased DNA methylation levels in *Gabra5* CpG island in males but no changes were found in females. Together, these results suggest that α_5GABA_A receptors mediate neuropathic pain in a sex-dependent fashion in rodents, which could be related to a sex-dependent *Gabra5* gene regulation in response to nerve injury. Estrogen receptor activation by 17β-estradiol is involved in α_5GABA_A receptors actions in neuropathic pain possibly through the modulation of epigenetic mechanisms to regulate *Gabra5*. The use of inverse agonists of α_5GABA_A receptors may be a viable strategy for treating neuropathic pain in women.

Disclosures: Ú. Franco-Enzástiga: None. **A.B. Salinas-Abarca:** None. **R. González-Barrios:** None. **B. Sánchez-Hernández:** None. **P. Barragan-Iglesias:** None. **G. García:** None. **J. Murbartian:** None. **T.J. Price:** None. **R. Delgado-Lezama:** None. **V. Granados-Soto:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.05/J26

Topic: D.03. Somatosensation – Pain

Title: Anti-allodynic effect of the combination tramadol and N-palmitoylethanolamide in rats with chronic constriction of the sciatic nerve

Authors: *Y. BLANCO HERNANDEZ, L. C. MENA VALDÉS, F. J. LÓPEZ MUÑOZ; CINVESTAV, Mexico City, Mexico

Abstract: Neuropathic pain (NP) is a chronic disorder with a complex and multifactorial etiology. Among drugs used in the NP treatment is tramadol (TRAM), a prototype of analgesic opioid drug. Moreover, it has recently described the antinociceptive effects of the cannabinoids for example N-palmitoylethanolamide (PEA). **Objective.** To evaluate the anti-allodynic effects of TRAM, PEA and the combination in rats with chronic constriction of the sciatic nerve (CCI model). **Methods**. Single doses of TRAM (3.16-31.62 mg/Kg, p.o), PEA (0.316-10.00 mg/Kg, p.o.) and the corresponding combinations were administered, from which the dose response curves were constructed. The antiallodynic effect was determined using the cold allodynia test in the CCI model. The evaluations were made up to 10 days after the surgery at 30, 60, 90, 120 and 180 minutes after the administration of the drugs. **Result.** It was found that TRAM, PEA and the combination showed anti-allodynic efficacy significative respect as the control group ($p<0.05$). Different combinations have been evaluated which have shown additive and potentiation effects. Of them the combination of TRAM 3.16 mg/Kg +PEA 0.316 mg/Kg presents an effect of potentiation which does not present significant differences ($p> 0.05$) with higher doses evaluated of the combination. **Conclusions.** These results demonstrate that the TRAM, PEA and the combination have anti-allodynic effect in rats with NP induced by CCl, and the combination of TRAM 3.16 mg/Kg +PEA 0.316 mg/Kg evidence potentiation effects.

Disclosures: Y. Blanco Hernandez: None. **L.C. Mena Valdés:** None. **F.J. López Muñoz:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.06/J27

Topic: D.03. Somatosensation – Pain

Support: R01NS045954
R01DA037621

Title: Inhibition of neuropathic pain via NPY Y1 receptor activation in the dorsal horn

Authors: *T. S. NELSON[1], D. F. S. SANTOS[1], K. E. MCCARSON[2], B. K. TAYLOR[1]; [1]Dept. of Anesthesiol. and Perioperative Medicine, Pittsburgh Ctr. for Pain Research, Pit, Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Univ. of Kansas Med. Ctr., Kansas City, KS

Abstract: Neuropeptide Y (NPY) exhibits long-lasting inhibitory control of nociceptive transmission after injury (Solway et al., 2011) but the specific receptor targets of NPY in the spinal cord have not been well characterized, particularly in the setting of neuropathic pain. Dorsal horn neurons that express the neuropeptide Y1 receptor (Y1R), an inhibitory G protein-coupled receptor, are well positioned to mediate the anti-nociceptive actions of NPY. We hypothesized that **f**ollowing peripheral nerve injury, Y1Rs maintain their functional G-protein coupling and that selective Y1R agonists will reduce behavioral symptoms of neuropathic pain and immunohistochemical markers of central sensitization in cells in the dorsal horn. Male and female C57BL/6 mice underwent spared nerve injury surgery (SNI), a model of neuropathic pain. First, [^{35}S]GTPγS binding assays in lumbar spinal cord sections of both sham and SNI mice suggest that Y1R signaling efficacy remains intact within spinal neurons as neither the EC_{50} nor the E_{max} were affected by SNI ($p<0.05$, n=6-9). Second, intrathecal (i.t.) administration of the selective Y1R agonist, $Leu^{31}Pro^{34}$, dose-dependently reduces both mechanical (von Frey method) and cold (withdrawal duration to acetone droplet evaporation) hypersensitivity 14-28 days after SNI ($P<0.05$, n=8-11). Third, Y1R specific activation was determined by coadministration of $Leu^{31}Pro^{34}$ with a Y1R antagonist, which blocked the antihyperalgesic effects of $Leu^{31}Pro^{34}$ ($P>0.05$, n=4-7), whereas coadministration with a Y2 receptor antagonist did not ($P<0.05$, n=6-10). Lastly, pERK expression was assessed after the following steps: i.t. administration of drug (Y1 agonist, Y1 antagonist, Vehicle, or Y1 Agonist +Y1 Antagonist); 30-minute wait, 5 minutes of light brush mechanical stimulation of the injured hindpaw, and then perfusion. Spinal cord sections were processed for immunohistochemistry and the number of pERK-expressing cells in laminae I-III of L4 dorsal horn was quantified. $Leu^{31}Pro^{34}$ significantly reduced the number of pERK-expressing cells in the superficial dorsal horn ($P<.05$, n=4-6) but not when coadministered with a Y1R antagonist ($P>.05$, n=4-6). These results suggest that following SNI, the Y1R maintains the capacity to inhibit pain and that i.t. administration of a Y1R specific agonist reduces behavioral and molecular signs of central sensitization of pain-related dorsal horn neurons. In combination with previous studies these results support the Y1R as a promising target for the treatment of neuropathic pain and warrant clinical trials for the i.t. administration of Y1R-selective agonists.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.07/J28

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: Analgesic effects of a fish skin preparation on chemotherapy-induced neuropathic pain in rats

Authors: *H. KIM[1], S.-H. HWANG[1], P. YANG[2], J. M. AL-HASSAN[3], S. ABDI[1];
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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. However, many chemotherapeutic drugs including taxanes, vinca alkaloids, and platinum complexes produced chronic neuropathic pain, called chemotherapy-induced neuropathic pain that is a dose-limiting adverse effect which affects the quality of life of the cancer patients and survivals. The catfish *Arius bilineatus, Val.* secretes a proteinaceous epidermal secretion, preparations from which were reported to produce wound healing and anti-inflammatory activity. Fraction-B is a preparation from the skin secretions. The purpose of study was to determine the analgesic effects of Fraction-B on paclitaxel (PAC)-induced neuropathic pain (PINP) in rats. PINP was produced by intraperitoneal injections of PAC at a dose of 2 mg/kg on days 0, 2, 4, and 6 (total 8 mg/kg) in adult male Sprague Dawley rats. The pain behavioral test was measured by using a set of von Frey filaments and then calculated a 50% mechanical threshold. Western blotting of the L1-6 dorsal root ganglia (DRGs) was performed for the measurement of protein levels of pro-inflammatory mediators. Fraction-B was intraperitoneally injected after fully developed pain behavior. PAC induced mechanical allodynia, which began to manifest on days 7-10, peaked within 2 weeks, and plateaued for at least 2 months after the first PAC injection. PAC also increased the levels of pro-inflammatory mediators including phosphorylated nuclear factor κB and monocyte chemoattractant protein-1 in the DRGs. Systemic injection of Fraction-B ameliorated pain behaviors at doses of 3, 5, and 10 mg/kg. The 10 mg/kg of Fraction-B significantly increased mechanical threshold for 2 hours. Fraction-B decreased PAC-induced pro-inflammatory mediators. We conclude that Fraction-B alleviates chemotherapy-induced neuropathic pain in rats by reducing the levels of pro-inflammatory mediators in the DRGs.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.08/J29

Topic: D.03. Somatosensation – Pain

Title: Effect of 5-HT7 receptor agonist on chronic pain associated co-morbid disorders in neuropathic rats

Authors: *V. GOURA[1,2], P. JAYARAJAN[1], A. KISHORE[2], R. ABRAHAM[1], A. VUYYURU[1], R. NIROGI[1];
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Abstract: Chronic pain is a debilitating syndrome. Patients also suffer from mood disorders like depression, anxiety and cognitive deficits. Thus, treating chronic pain is becoming difficult task with the existing therapy. It is important to treat both pain and its associated disorders concurrently in co-morbid populations. Preclinical research is concentrated on G-protein coupled receptor (GPCR) classes in treating pain and associated depression. We have sought to put our efforts in characterizing a newly identified GPCR, the serotonin receptor subtype 7 (5-HT_7). As per literature survey LP-211, a 5-HT_7R agonist showed its therapeutic effects on sleep, anxiety, depression and pain in preclinical animal models. But till date, no data is available on pain co-morbidities. In the current study we tested LP-211, 1 and 3 mg/kg, i.p. and LP-211, 3 mg/kg, i.p. + Gabapentin 10 mg/kg, i.p. on partial sciatic nerve induced neuropathic pain (PSNL), streptozocin induced diabetic neuropathic pain (DNP) models and associated co-morbidities like anxiety, depression and cognitive deficits. Von Frey monofilaments were used for evaluating pain, elevated plus maze (EPM) for anxiety, forced swim test (FST) for depression and novel object recognition test (NORT) for cognition. LP-211, 3 mg/kg, i.p. showed mild analgesic effects in PSNL and DPN rats. LP-211, 3 mg/kg, i.p. + Gabapentin, 10 mg/kg, i.p. showed significantly synergistic analgesic effect in the current tested models for pain and in treating its associated disorders. Thus, LP-211 a 5-HT_7R agonist in combination with gabapentin would be a promising therapy for treating chronic pain.

Disclosures: **V. Goura:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Kishore:** A. Employment/Salary (full or part-time):; Manipal Academy of Higher Education. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Vuyyuru:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.09/J30

Topic: D.03. Somatosensation – Pain

Title: Assessment of the efficacy of different pharmacological treatments in a model of partial meniscectomy-induced osteoarthritis in female rats

Authors: A. ZANON, V. MAFFRE, Y. DARBAKY, *L. DIOP;
ANS Biotech, RIOM, France

Abstract: Osteoarthritis (OA) is a degenerative disease involving several joint tissues, characterized by damages to the articular cartilage. The partial meniscectomy model presents similarities to human OA with cartilage damage, subchondral bone remodeling, and presence of osteophytes. Symptomatically, the partial meniscectomy model has been described as inducing evoked pain (tactile allodynia). The objective of this study was to evaluate the activity of different pharmacological treatments (opioid receptor agonists, nonsteroidal anti-inflammatory drug (NSAID) and local anaesthetic) on mechanical allodynia in a model of partial meniscectomy-induced OA in female rats.
Methods: Adult female Lewis rats were anesthetized before partial resection of medial meniscus. On week 3 after surgery, animals received an acute administration of Morphine, Diclofenac or 0.9% NaCl. On week 6 after surgery, animals received an acute administration of Tramadol, Bupivacaine or 0.9% NaCl. Tactile sensitivity of both hindpaws was measured before and after treatment, on week 3 and 6, using electronic Von Frey.
Results: Partial meniscectomy surgery induced, from 3 weeks to 6 weeks after partial resection of medial meniscus, a reduced and stable paw withdrawal threshold in the vehicle-treated group as compared to the sham-operated controls. On week 3, a single subcutaneous administration of Morphine 3 mg/kg induced, in dose and time related manner, an antiallodynic effect in a model of partial meniscectomy-induced OA. In the same experimental conditions, Diclofenac 30 mg/kg po exhibited moderate antiallodynic effect. On week 6, a single oral administration of Tramadol 100 mg/kg produced, in dose and time related manner, a marked antiallodynic effect. Bupivacaine intra-articularly administered at 0.01 mg/kg did not induce any significant effect in a model of partial meniscectomy-induced OA.
Conclusions: In the model of partial meniscectomy-induced OA, opioid receptor agonists showed marked antiallodynic effects. The hypersensitivity was reduced by treatment with a NSAID but not with local anaesthetic in the model of OA.

Disclosures: **A. Zanon:** A. Employment/Salary (full or part-time):; ANS Biotech. **V. Maffre:** A. Employment/Salary (full or part-time):; ANS Biotech. **Y. Darbaky:** A. Employment/Salary (full or part-time):; ANS Biotech. **L. Diop:** A. Employment/Salary (full or part-time):; ANS Biotech.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.10/J31

Topic: D.03. Somatosensation – Pain

Title: Investigation of the temporal plasma cytokine/chemokine profile of the monosodium iodoacetate rat model of osteoarthritis: Relevance to pharmacological reversal of hyperalgesia

Authors: *J. A. PRENDERVILLE[1], E. SOKOLOWSKA[1], M. BIANCHI[1], A. L. THOMAS[2], C. MONTAGUT-BORDAS[3], A. S. FISHER[2], N. UPTON[2], A. H. DICKENSON[4]; [1]Transpharmation Ireland Ltd, Dublin, Ireland; [2]Transpharmation Ltd, London, United Kingdom; [3]Neuroscience, Physiology, Pharmacol., Univ. Col. London, Dublin, Ireland; [4]Univ. Col. London, London, United Kingdom

Abstract: Osteoarthritis (OA) is estimated to affect 10-15% of individuals over the age of 60 (WHO, 2013). OA primarily affects load bearing joints, including the knee, often leading to pain and disability. Identification of a plasma biomarker to predict pharmacological efficacy will facilitate drug discovery in OA. We have used the monosodium-iodoacetate (MIA) rat model of OA to investigate plasma cytokine/chemokine profile after OA induction. The OA model was induced in 3 cohorts of male Sprague-Dawley rats (n=105) by intra-articular injection (knee joint) of MIA (glycolysis inhibitor; 80mg/ml, 25ul). Weight-bearing was measured using an incapacitance meter at baseline and hyperalgesia induced by MIA was calculated. Cohort 1 received daily injections of vehicle, celecoxib (50mg/kg) or pregabalin (30mg/kg) on days 3-7 (early phase). Cohort 2 received the same treatments on days 24-28 (late phase). Hyperalgesia was measured daily and compared with sham control. In cohort 3 plasma was sampled at baseline and 4, 7 and 14 days after MIA administration. IFN-γ, IL-1β, IL-4, IL-5, IL-6, KC/GRO, IL-10, IL-13 and TNF-α were analysed. MIA resulted in an approximate 70% reduction in weight-bearing on the ipsilateral side. In cohort 1, the reduction in weight-bearing was reversed by celecoxib, pregabalin had no effect. In cohort 2, the reduction in weight-bearing was reversed by pregabalin, celecoxib had no effect. In cohort 3, plasma KC/GRO was increased at day 4 in comparison to baseline. TNF-α was decreased on day 7 and day 14 in comparison to day 4. IL-4 and IL-10 were increased at day 14. This study supports the previously reported biphasic nature of the MIA model, characterised by the early inflammatory phase where hyperalgesia is reversed by the non-steroidal anti-inflammatory drug (NSAID) celecoxib and the late neuropathic phase showing sensitivity to pregabalin. Consistent with this, we show acute early elevation of the chemokine KC/GRO and a progressive decrease in the inflammatory cytokine TNF-α across the inflammatory phase. The anti-inflammatory cytokines IL-4 and IL-10 were increased after the inflammatory phase. These data suggest that plasma inflammatory markers may indicate OA disease progression and could be used to inform treatment strategy.

Disclosures: J.A. Prenderville: A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **E. Sokolowska:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **M. Bianchi:** A. Employment/Salary (full or part-time):; Transpharmation Ireland Ltd. **A.L. Thomas:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **C. Montagut-Bordas:** None. **A.S. Fisher:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **N. Upton:** A. Employment/Salary (full or part-time):; Transpharmation Ltd. **A.H. Dickenson:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.11/J32

Topic: D.03. Somatosensation – Pain

Title: Anti-inflammatory and anti-nociceptive activities of Montanoa tormentosa topical preparation in Wistar rats

Authors: *I. E. JUAREZ-ROJOP[1], G. E. VILLAR-JUAREZ, Jr[1,2], C. A. TOVILLA-ZARATE[1], D. E. AGUILAR-DOMINGUEZ[1], A. M. ZETINA-ESQUIVEL[1], J. C. DIAZ-ZAGOYAZ[1,3], J. L. BLE-CASTILLO[1], T. RAMON-FRIAS[1];
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Abstract: *Montanoa tomentosa* is widely known in Mexico for treating female health disorders since hundreds of years, yet there are no scientific report about its use on pain or inflammation even when certain population of the country has given the plant this use. Thus, in this study we used the formalin test and the carrageenan-induced edema to test the antinociceptive and anti-inflammatory effect of an ointment containing hidroalcoholic extract of *M. tomentosa;* furthermore, we performed the histological examination of tissue from all treatments to describe the inflammatory response and the histopathologic changes on each treatment. Our results showed that topical administration of MT (*M. tomentosa*) ointment diminished flinching behavior induced by formalin and significantly reduced the carrageenan-induced edema. Besides, we observed a significant reduction in tissue disruption as well as less infiltration of leucocytes when the dose 50 mg/paw was administered. These data suggest that MT ointment has interesting and potential antinociceptive and anti-inflammatory activities.
Keywords
zoapatle, anti-inflammatory, antinociceptive, ointment, *Montanoa tomentosa*

Disclosures: I.E. Juarez-Rojop: None. **G.E. Villar-Juarez:** None. **C.A. Tovilla-Zarate:** None. **D.E. Aguilar-Dominguez:** None. **A.M. Zetina-Esquivel:** None. **J.C. Diaz-Zagoyaz:** None. **J.L. Ble-Castillo:** None. **T. Ramon-Frias:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.12/J33

Topic: D.03. Somatosensation – Pain

Support: CONACyT 226454
CONACyT 256448
INP17073.0.

Title: Antihyperalgesic and antiallodynic activities of the rosmarinus officinalis oil nanoemulsion in a fibromyalgia model in rats

Authors: *A. HERNÁNDEZ LEÓN[1], M. E. GONZÁLEZ-TRUJANO[1], J. C. TAVARES-CARVALHO[2], A. NAVARRETE[3];
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Abstract: Fibromyalgia (FM) is a musculoskeletal chronic pain syndrome in humans due to an altered processing of somatosensory information. No efficacious current therapy strongly promotes strategies for its treatment or attenuation. *Rosmarinus officinalis* is an ancient medicinal plant with a long history and scientific studies supporting its potential antinociceptive properties. The aim of this study was to investigate the effects of *R. officinalis* essential oil alone and prepared in a nanoemulsion formulation, to compare Mexican and Brasilian plants, using the reserpine (RES)-induced FM like pain model in rats. Male Wistar rats weighing 200 to 250 g were grouped in n=6 animals. The behavioral thresholds of nociceptive response in the experimental FM were analyzed in parameters of muscular hyperalgesia, and tactile and cold allodynia. Groups consisted in: (a) No treatment (healthy control), (b) FM, (c) FM + nanoemulsion *R. officinalis* essential oil (RO) from Mexican plant (NEMEX), (d) FM + nanoemulsion RO from Brazil plant (NECHA), both at 5% concentration, compared to the (e) RO without nanoemulsion at a dosage of 100 mg/kg as reference sample or a standardized nanoemulsion (NECULT) at 5% and 20%. Our results demonstrated that conventional obtention of RO from Mexican plant produced significant antihyperalgesic and antiallodynic responses. The antihyperalgesic but not antiallodynic response was resembled by nanoemulsions of RO obtained from Brazil or Mexican plants. In conclusion, our results give evidence that *R. officinalis* oil possesses potential as alternative treatment for FM-like pain which antihyperalgesic dosage might be improved by using a nanoemulsion formulation

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Poster

483. Pain Models: Pharmacology

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Program #/Poster #: 483.13/J34

Topic: D.03. Somatosensation – Pain

Support: CONACyT 226454
CONACyT 256448
INP17073.0

Title: Potential analgesic-like effects of Tilia americana var. mexicana in an experimental animal model of fibromyalgia

Authors: *Y. E. QUINTO-ORTIZ[1], A. HERNANDEZ-LEON[2], L. D. PALOMINO-NAVARRETE[3], M. E. GONZALEZ-TRUJANO[2];
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Abstract: Fibromyalgia (FM) is a painful syndrome characterized by chronic generalized pain and central nervous system comorbidity. Its prevalence is higher in women than in men. Although drugs are available to alleviate most of the symptoms, their adverse effects promote discontinuation of drug therapy. Therefore, it is preponderant to find alternatives of therapy efficacious and safety. In the present investigation, a methanol extract of *Tilia americana* var. *mexicana* was studied to give evidence of its potential as therapeutic alternative for FM. Ethno-pharmacological knowledge of this species in traditional Mexican medicine have described significant analgesic and anxiolytic and sedative-like effects because of the presence of flavonoid compounds. The experimental model of reserpine-induced FM was applied using female Wistar rats (200-250 g). Analgesic-like effect of *Tilia* (10, 30, and 100 mg/kg i.p.) and their fractions (AB: 100 mg/kg i.p., F: 10, 30, 100, and 300 mg/kg) obtained by chromatographic analysis were explored compared to those observed with the reference drug fluoxetine (10 mg/kg s.c., 3 injections -24, -5 and 0 h before the test) and tramadol (10 mg/kg i.p.). The combination of AB-fraction (rich in terpenes) or F-fraction (rich in flavonoids) with fluoxetine (2.5 mg/kg s.c. 3 injections -24, -5 and 0 h before the test) or tramadol (3 mg/kg i.p.) was also explored to look for a pharmacological synergistic interaction. Data demonstrated that *Tilia* extract and fractions alone produced antihyperalgesic and antiallodynic-like effects since they increased thresholds to the muscular pressure in about 56-91%, tactile allodynia in 80-87%, and in cold allodynia in 82-100%. Combination of AB or F- fractions with fluoxetine or tramadol produced lower effects than those observed in individual administration suggesting an antagonic pharmacological interaction. In conclusion, this study gives evidence that *Tilia americana* var. m*exicana* extract

possess constituents with potential properties to alleviate pain-like FM, however caution is important in combination of alternatives of therapy since a drug interaction is highly probably.

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Poster

483. Pain Models: Pharmacology

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Program #/Poster #: 483.14/J35

Topic: D.03. Somatosensation – Pain

Support: Conacyt CB-2012/179294

Title: Spinal dopaminergic receptors contribute to nociception in a rat model of fibromyalgia

Authors: *Y. E. DE LA LUZ-CUELLAR[1], F. MERCADO[2], V. GRANADOS-SOTO[1]; [1]Dept. de Farmacobiología, CINVESTAV Sede Sur, Ciudad de Mexico, Mexico; [2]Dirección de Investigaciones en Neurociencias, INPRFM, Ciudad de Mexico, Mexico

Abstract: Fibromyalgia patients have reduced levels of monoamines in cerebrospinal fluid and this could lead to a dysfunction of descending pain modulation systems. Spinal dopaminergic projections from the hypothalamic A11 nucleus modulates nociceptive transmission in dorsal horn of spinal cord. Activation of central and peripheral D2-like receptors produces anti-nociceptive effects while stimulation of D1-like receptors increase neuronal excitability and has pro-nociceptive effects in models of inflammatory and neuropathic pain. However, the role of spinal dopaminergic receptors in functional pain is unknown. The aim of this study was to investigate the role of spinal dopamine receptors in a reserpine-induced model of fibromyalgia. Fibromyalgia-type nociception was induced by a reserpine injection (1 mg/kg) for three consecutive days in female Wistar rats. Tactile allodynia (TA) and muscular hyperalgesia (MH) were assessed with Von Frey filaments and the Randall-Selitto test, respectively. Reserpine-treated rats were intrathecally injected with the selective D2-like agonists quinpirole (1-10 nmol), and pramipexole (0.15-15 nmol), or the D1-like receptor antagonist SCH-23390 (10-100 nmol). Rats also were treated with intrathecal co-treatments of quinpirole or pramipexole and selective antagonists for D2 (L-741,626), D3 (PG01037) and D4 (L-745,870) receptors. Similarly, reserpinized rats received intrathecal co-treatment of SCH-23390 with the D1-like agonist SKF-38393. Experimenter was blinded to all treatments. Intrathecal quinpirole and pramipexole, but not vehicle, partially reversed reserpine-induced TA and MH in a dose-dependent manner. Co-treatment with L-741,626 totally reversed the anti-allodynic and anti-hyperalgesic effects of quinpirole and pramipexole, whilst co-treatments with PG01037 and L-745,870 moderately blocked the anti-nociceptive effects of these compounds. These data suggest

that activation of spinal D2-like receptors has anti-nociceptive effects in fibromyalgia-like nociception, with a major role of D2 receptor-subtype. Moreover, intrathecal SCH-23390, but not vehicle, completely reversed TA and partially reversed MH in reserpinized rats. Co-treatment with SFK-38393 completely reversed the anti-allodynic effect of SCH-23390, suggesting that activation of D1-like receptors has a pro-nociceptive effect in fibromyalgia-like nociception. The D1-like agonist and all D2-like antagonists had no effect *per se*. Results suggest that spinal dopaminergic receptors, mainly through the activation D1-like receptors, contribute to the nociceptive hypersensitivity induced by reserpine in female rats.

Disclosures: Y.E. De La Luz-Cuellar: None. **F. Mercado:** None. **V. Granados-Soto:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.15/J36

Topic: D.03. Somatosensation – Pain

Support: NIH Grant K99HL133590
NIH Grant R35HL140031

Title: Protein kinase C-beta isoform as a mechanism promoting chronic pain in sickle cell disease

Authors: *Y. HE[1], Z. J. WANG[2];
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Abstract: As a marker of disease severity and mortality predictor, pain is one of the most dreadful symptoms in sickle cell disease (SCD) and is refractory to currently available analgesics. Besides acute painful vaso-occlusive crises, SCD is also accompanied by intractable chronic pain. This persistent, and often unrelieved, pain starts early in childhood and continues throughout life. The neurobiological mechanisms of chronic pain in SCD remain unclear, which markedly limits effective pain management and the quality of life in patients with SCD. Taking advantage of a humanized mouse model of SCD, this study aimed to investigate protein kinase C (PKC)-beta isoform mechanism for chronic pain in SCD. We characterized pain phenotypes in the Townes' mouse model (TOW) of SCD that exclusively expresses human alleles encoding normal α- and sickle β-globin. TOW mice exhibited ongoing spontaneous pain as well as hypersensitivity to evoked pain stimuli compared with littermate control mice. We then examined spinal and nociceptor PKCbeta-mediated signaling and behavioral consequences. Prominent activation of PKCbeta was identified in the superficial laminae of the spinal cord dorsal horn as well as in the nociceptors in TOW sickle mice. Functional inhibition and genetic silencing of the PKC isoform attenuated sickle cell pain phenotypes, abolishing PKC activation,

spontaneous pain, mechanical allodynia, and heat hyperalgesia in the sickle cell mice. Taken together, these data suggest PKCbeta as one of the mechanisms for the generation and maintenance of ongoing and evoked pain in SCD. These findings offer insights into sickle cell pain mechanisms, which may become a potential target for pharmacological interventions.

Disclosures: Y. He: None. **Z.J. Wang:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

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Program #/Poster #: 483.16/J37

Topic: D.03. Somatosensation – Pain

Support: 18H02897
18K16475
16K20084

Title: Opioid-induced hyperalgesia by chronic administration of morphine is caused by serotonin in spinal dorsal horn and, in part, through the 5HT-3 receptor

Authors: *Y. KAMIYA, M. SASAKI, M. TANAKA, K. BAMBA, T. OHNISHI;
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Abstract: [Introduction] We conducted the following experiments to clarify the involvement of serotonin and the 5HT-3 serotonin receptor in hyperalgesia induced by chronic opioid administration. [Method] This study was approved by the Niigata University Animal Experiment Ethics Committee (Approval No. H27-203). We created the following groups using male C57BL / 6 mice (6-9 weeks old); a group that received 20 mg / kg of morphine hydrochloride intraperitoneally twice a day for 4 days, a group in which serotonin synthesis inhibitor para-chlorophenylalanine (PCPA) 150 mg / kg was administered once a day from 4 days before morphine administration through the morphine administration period, a group in which a 5HT-3 receptor antagonist ondansetron (OND) 2 mg / kg was administered 30 minutes before morphine administration. The Paw withdrawal thresholds were measured by von Frey test for these groups. Moreover, in the spinal dorsal horn of the above three groups, expression levels of phosphorylated ERK and glial fibrillary acidic protein (GFAP), which are known to be activated by nociceptive stimuli at spinal dorsal horn, and serotonin were compared using immunostaining. [Results] Four days of continuous administration of morphine produced paw withdrawal hyperalgesia, but no hyperalgesia occurred in the PCPA-treated group. Moreover, pre-administration of OND suppressed hyperalgesia (control group (n = 9): 1.04 ± 0.1 g, morphine group (n = 11): 0.34 ± 0.06 g, morphine + PCPA group (n = 8): 1.04 ± 0.08 g, morphine + OND 2 mg / kg: 0.73 ± 0.11 g, $p < 0.001$ by Kruskal -Wallis test). Continuous administration of

morphine apparently increased serotonin expression in the spinal dorsal horn, but PCPA administration completely suppressed the increase of serotonin expression by morphine administration. On the other hand, co-administration of OND did not suppress the increase of serotonin by the morphine administration. Morphine administration significantly increased phosphorylated ERK and GFAP but was significantly suppressed by PCPA and OND treatment. [Conclusion] The present study suggested that chronic administration of morphine to mice causes hyperalgesia, which involves serotonin, and a part of which is mediated by the 5HT-3 receptor.

Disclosures: Y. Kamiya: None. **M. Sasaki:** None. **M. Tanaka:** None. **K. Bamba:** None. **T. Ohnishi:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.17/J38

Topic: D.03. Somatosensation – Pain

Support: Sally McDonnell Barksdale Honors College
National Center for Natural Products Research

Title: The role of cannabinoids and terpenes in cannabis-mediated analgesia in rats

Authors: *K. J. SUFKA[1,2], H. M. HARRIS[1], M. A. ROUSSEAU[2], A. S. WANAS[1], M. M. RADWAN[1], S. CALDWELL[2], *K. J. SUFKA[3,1], M. A. ELSOHLY[1,4];
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Abstract: Cannabis sativa has been used for centuries in treating pain. However, the analgesic role of many of its constituents including the terpenes is unknown. This research examined the contributions of terpenes (volatile oil) and cannabinoids in cannabis-mediated analgesia in rats. Animals received intraperitoneal administration of either vehicle, 10.0 or 18.0 mg/kg morphine, or various doses of the extract without terpenes, isolated terpenes, THC, or the full extract. 30 m later animals were tested on hotplate and tail-flick tests of thermal nociception. One week later, rats received a second administration of test articles and tested 30 m later in the abdominal writhing test of inflammatory nociception. In the thermal assays, hotplate and tail-flick latencies for morphine treated rats were dose-dependent and significantly higher than vehicle treated animals. All of the cannabinoid compounds except for the isolated terpenes produced dose-dependent increases in hotplate and tail-flick latencies. In the inflammatory nociceptive assay, animals treated with vehicle and isolated terpenes demonstrated increased abdominal writhing

while all of the cannabinoid compounds significantly decreased abdominal writhing responses. Overall, THC alone produced robust analgesia equivalent to the full cannabis extract while terpenes alone did not produce analgesia. These data suggest the analgesic activity of cannabis is largely mediated by THC while terpenes alone do not cause alterations in cannabis-mediated analgesia.

Disclosures: **K.J. Sufka:** None. **H.M. Harris:** None. **M.A. Rousseau:** None. **A.S. Wanas:** None. **M.M. Radwan:** None. **S. Caldwell:** None. **K.J. Sufka:** None. **M.A. ElSohly:** None.

Poster

483. Pain Models: Pharmacology

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Program #/Poster #: 483.18/J39

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DA25267
NIH Grant DA48353

Title: The marijuana-derived terpene β-Caryophyllene reverses mechanical allodynia and thermal hyperalgesia in a mouse model of neuropathic pain

Authors: *J. L. WILKERSON[1], J. S. FELIX[2], L. R. MCMAHON[1];
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Abstract: Pain is one of the most common reasons to seek medical attention and chronic pain is a worldwide epidemic. Under some circumstances, incoming protective nociceptive signaling is prolonged leading to behavioral sensory alterations common to pathological neuropathic pain. As marijuana contains numerous terpenes, we hypothesized that the terpene β- Caryophyllene would reverse behaviors associated with pathological neuropathic pain. We used the chronic constriction injury of the sciatic nerve (CCI) model of neuropathic pain, which produces robust increases in sensitivity to light mechanical touch, or allodynia, as assessed with von Frey filaments, and increased thermal sensitivity, or thermal hyperalgesia, as assessed in the hotplate test. To examine the involvement of cannabinoid receptors, we also tested this compound in mice that had undergone the CCI surgery that lack either functional cannabinoid type 1 receptors (CB_1R (-/-)) or mice lacking functional cannabinoid type 2 receptors (CB_2R (-/-)).
First, we assessed the ability of β- Caryophyllene to reverse mechanical allodynia and thermal hyperalgesia. Male and female wildtype mice on a C57BL/6J background underwent CCI surgery with chromic gut suture used to ligate the sciatic nerve. Sham mice underwent surgical procedures but without nerve ligation. Starting seven days after surgery, mice were injected intraperitoneally (i.p.) with a single dose of vehicle (1 part ethanol / 1 part emulphor/ 18 parts saline) or β- Caryophyllene (56, 100, 178 mg/kg) and 20 min later mice were tested for

mechanical allodynia and thermal hyperalgesia. Mice in the CCI - Vehicle group displayed robust mechanical allodynia and thermal hyperalgesia when compared to Sham - Vehicle mice. The terpene β- Caryophyllene produced dose-dependent reversal of mechanical allodynia at the doses of 100 and 178 mg/kg, and dose-dependent reversal of thermal hyperalgesia at the dose of 178 mg/kg. Next, we tested β- Caryophyllene at the dose of 178 mg/kg (i.p.) in male and female CB_1R (-/-), CB_2R (-/-) mice. In CB_2R (-/-) mice this dose was not sufficient to reverse mechanical allodynia, or thermal hyperalgesia. Meanwhile, in CB_1R (-/-) no attenuation of β-Caryophyllene's effects on mechanical allodynia or thermal hyperalgesia was observed. This demonstrates that CB_2R are necessary for β- Caryophyllene's anti- allodynic and thermal hyperalgesic effects, with CB_1R being dispensable. These findings suggest that β- Caryophyllene acts via CB_2R and may be an attractive therapeutic for the treatment neuropathic pain.

Disclosures: J.L. Wilkerson: None. **J.S. Felix:** None. **L.R. McMahon:** None.

Poster

483. Pain Models: Pharmacology

Location: Hall A

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Program #/Poster #: 483.19/J40

Topic: D.03. Somatosensation – Pain

Support: JSPS KAKENHI Grant Number 17K11535

Title: The role of spinal endocannabinoids in a rat model of oro-facial neuropathic pain

Authors: *K. NAKAI[1], A. NAKAE[2], Y. MINEGISHI[1], R. URABE[1], M. MIYAMAE[1], T. YANAGIDA[2], K. HOSOKAWA[3], T. KUBO[4];
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Abstract: Background: Endocannabinoids are decomposed by enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL). Inhibitors for FAAH and MAGL increase amounts of endocannabinoids. The manipulation of endogenous cannabinoids (CBs) is an alternative to the direct targeting of CB receptors for the treatment of pain. The contribution of spinal endocannabinoids in the oro-facial neuropathic pain remains unclear. Chronic constriction injury to the infraorbital nerve (ION-CCI) has proven to be a useful model for oro-facial neuropathic pain. The present study evaluates the role of spinal endocannabinoids in a rat model of oro-facial neuropathic pain. Material and Methods: Male Sprague Dawley rats underwent unilateral CCI to the right ION. The ION was dissected free in the orbital cavity. Two nylon (5-0) ligatures were loosely tied around the ION. 14 days after the initial surgery, tactile allodynia of the territory of the ligated nerve was confirmed by measuring the mechanical

response threshold in response to application of von Frey filaments. Only rats with hyper-responsiveness to mechanical stimulation were used. An intrathecal catheter was implanted for upper cervical spinal injection of drugs. The polyethylene tube (PE10) was advanced 10 mm caudally through a tiny hole in the atlantooccipital membrane and the dura. The animals were allowed to recover 7 days before drug testing. The time course of analgesic effects of intrathecally administered a FAAH inhibitor JNJ1661010 and a MAGL inhibitor JZL184 were examined. We evaluated the antagonizing effect of intrathecal pretreatment with a CB1 receptor antagonist SR141716A or a CB2 receptor antagonist AM630, on the analgesic action of the FAAH inhibitor or the MAGL inhibitor. The time course data for the dose-response effects were analyzed by two-way analysis of variance and Tukey-Kramer multiple-comparison test. Results: Intrathecal administration of JNJ1661010 and JZL184 significantly increased mechanical thresholds in a dose dependent manner. AM630 significantly reduced the analgesic effects of JNJ1661010 and JZL184. SR141716A did not alter the analgesic effects of JNJ1661010 and JZL184. Conclusions: The increase of spinal endocannabinoids reduced the pain-related behavior in a rat model of oro-facial neuropathic pain. The pain modulation was mediated by CB2 receptors.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.20/J41

Topic: D.03. Somatosensation – Pain

Title: High capacity *in vitro* disease modelling of chronic pain

Authors: *P. KARILA, C. NODIN, S. LARDELL, M. KARLSSON;
Cellectricon AB, Mölndal, Sweden

Abstract: Rodent models have been used extensively to provide insight into the mechanisms underlying many diseases, and to explore the efficacy of candidate drugs. Despite recent questioning of rodent models, they still bring immense value to the scientific community. For example, using a high capacity optical electrophysiology approach where up to 96 neuronal cultures can be probed in parallel, we have demonstrated that changes in neuronal excitability induced by long-term inflammation *in vivo* clearly persists after establishment of primary mouse dorsal root ganglia (DRG) cultures (Bersellini Farinotti et al. Abstract number 10283, Neuroscience 2018). Chemotherapy-induced peripheral neuropathy (CIPN) is a common adverse effect of commonly used chemotherapeutic drugs and there is a need for efficient and physiologically relevant screening methods to identify compounds reversing the neuropathy-

related adverse effects. In the current exploratory study, the purpose was to establish a high capacity testing approach for CIPN-inducing chemotherapeutic agents on neuronal excitability *in vitro*.Successful assay development would enable efficient screening of compounds reversing the effects induced by CIPN-inducing compounds and ultimately aid in understanding adverse effects of commonly used chemotherapeutic drugs such as platinum drugs and taxanes.
Rat DRGs were prepared according to previously described methods (Sidders et al. J Mol Biol. 2018 Sep 14;430(18 Pt A):3005-3015) and plated into 384-well plates. The CIPN-inducing compounds oxaliplatin and paclitaxel were added to the cultures up to seven days prior to evaluating the compound effects on an optical electrophysiology platform. The cultures were subsequently fixed to enable immunocytochemical investigation of neuronal morphology.
Oxaliplatin induced increased neuronal excitability in the rat DRG cultures. The effects were most pronounced after seven days. In contrast, in presence of paclitaxel, neuronal excitability was reduced in a concentration- and time-dependent manner. In addition to the functional effects, morphological parameters such as changes in the number of neurons and the extent of the neurite network were investigated for the two drugs.
In conclusion, by using our high capacity plate-based optical electrophysiology platform, we have developed models to explore and understand underlying conditions in the excitability properties of sensory neurons in disease conditions. The models can be used for large scale screening for compounds that are reversing the effects induced by CIPN-inducing compound. The translational aspects of the results will also be discussed.

Disclosures: **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB. **C. Nodin:** A. Employment/Salary (full or part-time):; Cellectricon AB. **S. Lardell:** A. Employment/Salary (full or part-time):; Cellectricon AB. **M. Karlsson:** A. Employment/Salary (full or part-time):; Cellectricon AB.

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.21/J42

Topic: D.03. Somatosensation – Pain

Support: NIH Grant NS065926
NIH Grant NS102161

Title: Spinal calcitonin gene-related peptide promotes chronic pain plasticity and depolarizes dorsal horn chloride reversal potentials in female but not male mice

Authors: *C. A. PAIGE[1], I. P. FERNANDEZ[2], M. KUMEO[1], M. PAPALAMPROPOULOU-TSIRIDOU[2], L.-E. LORENZO[2], G. L. MEJIA, JR[1], F. M. FERRINI[3], Y. DE KONINCK[4], G. DUSSOR[1], T. J. PRICE[1];

[1]Sch. of Behavioral and Brain Sci., Univ. of Texas At Dallas, Richardson, TX; [2]Cell. and Mol. Neurobio., Laval Univ., Quebec, QC, Canada; [3]Univ. of Turin, Grugliasco, Italy; [4]Cell. & Mol. Neurobio., Laval Univ. / IUSMQ, Quebec, QC, Canada

Abstract: The majority of patients impacted by chronic pain are women. In our study, we aimed to investigate the potentially sexually dimorphic role of Calcitonin Gene-Related Peptide (CGRP) in three mouse models of chronic pain: hyperalgesic priming, incision, and spared-nerve injury (SNI). Based on emerging findings from the migraine field, we hypothesized that CGRP antagonists would block all three forms of chronic pain specifically in female mice. We induced hyperalgesic priming with an injection of the human IL-6 receptor (IL-6r) or through an incision of the hindpaw. The spared nerve injury was used to induce neuropathic pain. In the hyperalgesic priming experiments CGRP8-37, a CGRP receptor antagonist, was given intrathecally (I.T.) at either the time of IL-6r/incision or PGE2 injection in order to determine if CGRP8-37 could block the establishment of or reverse hyperalgesic priming. For animals with SNI, CGRP8-37 was administered I.T. and PWT was measured following the I.T. injection. In priming induced by IL-6r injection, CGRP8-37 both blocked and reversed hyperalgesic priming specifically in females. In the incision model, CGRP8-37 blocked priming in female mice following PGE2 injection. In the SNI model, there was a transient effect of the CGRP antagonist on mechanical hypersensitivity in female mice only. Our findings demonstrate that blocking CGRP receptors with CGRP8-37 is effective in reducing mechanical hypersensitivity in all 3 models, but only in female mice. Consistent with these findings I.T. CGRP caused a long-lasting mechanical sensitivity specifically in female mice. This CGRP-induced mechanical hypersensitivity was reversed by the KCC2 activator, CLP-257. However, in the IL-6r induced hyperalgesic priming model I.T. CLP-257 reversed hyperalgesic priming in both male and female animals. In spinal dorsal horn electrophysiology experiments CGRP shifted chloride reversal potentials to significantly more positive values but, again, only in female mice. Therefore, CGRP may regulate KCC2 expression and/or activity specifically in females but KCC2 clearly plays a role in promoting mechanical pain hypersensitivity in both sexes. We conclude that CGRP promotes pain plasticity in female mice, but has a limited impact in male mice, suggesting that CGRP antagonists may be an effective treatment for many forms of chronic pain in females.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.22/J43

Topic: D.03. Somatosensation – Pain

Title: HC-030031, TRPA1 antagonist, produced efficacy in AITC-induced pain despite low theoretical receptor occupancy

Authors: M. HAJOS[1], R. GILFILLAN[1], J. P. GILBERT[1], M. CHAMBERS[2], A.-M. KÄRKKÄINEN[3], S. ROBJOHNS[2], E. LOWE[2], G. CLARK[2], S. WILLIAMS[2], S. MAIDMENT[2], ***D. MISZCZUK**[3];
[1]Biogen, Cambridge, MA; [2]Charles River Discovery, Saffron Walden, United Kingdom; [3]Charles River Discovery, Kuopio, Finland

Abstract: Effective treatment of chronic pain remains an unmet medical need. Growing evidence supports the role of the transient receptor potential cation channel, sub-family A, member 1 (TRPA1) in the pathophysiology of neuroinflammatory and neuropathic pain. TRPA1 is highly expressed in primary nociceptive neurons of the trigeminal ganglion, and dorsal root ganglia, and is activated by noxious cold and natural irritants such as allyl isothiocyanate (AITC). HC-030031, a widely used TRPA1 antagonist, has demonstrated efficacy in acute and neuropathic pain models such as chemotherapy-induced polyneuropathy, spinal nerve ligation, Complete Freuds Adjuvant-induced pain and AITC-induced flinch in mice and rats.
In the current study we set out to characterize the pharmacological performance of HC-030031 against human and rat TRPA1 using robust *in vitro* screening assays. This data was used alongside plasma and brain concentrations to determine the theoretical receptor occupancy (%RO) required for an efficacious response in the AITC-induced flinch pain model.
The inhibitory properties of HC-030031 were tested in human and rat TRPA1 *in vitro* screening assays, with the FLIPR^{TETRA} calcium influx assays providing IC_{50} values of 5.2 and 12 µM, respectively. Electrophysiology assays using both automated (Sophion Qube) and manual patch-clamp confirmed HC-030031 potency. Selectivity against family members, TRPV1, TRPV4 and TRPM8, was observed using the FLIPR^{TETRA} (IC_{50} > 30 µM). Efficacy assessment of HC-030031 (3, 10, 30, 100 and 300 mg/kg, PTT 2h) in AITC-induced flinch in rats showed a decreased duration of flinch behavior following dosing at 10, 30, 100 and 300 mg/kg. Whilst HC-030031 displayed a dose proportional increase in plasma and brain exposure between 10 and 300 mg/kg there was no increase in PD response. Free plasma concentrations were 5-410 ng/ml (93% bound) and brain concentrations were 4-416 ng/g (91% bound).
The %RO based on free concentrations of HC-030031 was estimated to be <3% in both plasma and brain at all dose levels. Additionally, receptor occupancy was also low when calculated from total HC-030031 levels, with a PD response observed after 10 mg/kg dosing where <1% RO was predicted (free concentrations).
In conclusion, this data suggests that the *in vivo* efficacy based on the free plasma concentration in the AITC-induced flinch in rats cannot be explained by the TRPA1 inhibitory effect in isolation. The possible off-target mechanisms for HC-030031 efficacy remains to be investigated.

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Poster

483. Pain Models: Pharmacology

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.23/J44

Topic: D.03. Somatosensation – Pain

Support: SIP IPN Grant 20190023

Title: Antinociceptive profile of substituted phthalimides with aspartate enantiomers in rats

Authors: *E. RAMIREZ-SAN JUAN[1], C. CAMPOS-RODRIGUEZ[1,2], I. CUMBRES-VARGAS[1], A. PINEDA-PINEDA[1], R. M. AGUILAR-SANCHEZ[1], J. G. TRUJILLO-FERRARA[3];
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Abstract: Pain is related with almost all the clinical pathologies across all ages and sex, implicating a decrease in the quality of life of the patients and an economic problem within the countries. Consequently, finding new therapies or strategies to relief pain is relevant for the population. Pain could be defined as an unpleasant emotional and sensory experience, which is a direct output of nociception. In the market, a wide-variety of analgesic drugs have been sold but they are not solving the main problem. In the last decade, phthalimides derivatives called the attention due to their analgesic and anti-inflammatory properties. Thalidomide is the prototype of those molecules that have been emerged. An inhibition of the tumor necrosis factor alpha, interleukin 6 and 12 and the inhibition of the cyclooxygenases (mainly COX-2) are some of the implicated mechanisms of action suggested for the N-substituted phthalimide molecules. Previous studies in the lab, showed that symmetric phthalimides have antinociceptive and anti-inflammatory activity. Additionally, N-substituted phthalimides with aspartate demonstrated an NMDA antagonist profile in silico and in vivo. With this basis the aim of the study was to evaluate the antinociceptive and anti-inflammatory activity of N-substituted phthalimides with R or S aspartate (RTASP, STASP) in an acute (Tail-Flick test) and inflammatory (Formalin test) model of pain in rats. For this purpose, groups of adult Wistar male rats (250-300 g; n=8) were treated: a) dimethyl sulfoxide (DMSO) 2% in phosphate buffer solution (PBS, pH = 7, control), b) indomethacin 5 mg/kg (positive control) c) RTASP or STASP 100 mg/kg, d) RTASP or STASP 316 mg/kg, e) RTASP or STASP 421.7 mg/kg. After 45 min of the intraperitoneal administration, the tail flick test or formalin test were run. For the Tail-Flick test, the latency to the tail flick were measure, while for the formalin test, the number of flinches and area under a curve of flinches (AUC) were analyzed. The results evidenced that RTASP and STASP has antinociceptive effect due probably to their anti-inflammatory property. At the three proven

doses, both molecules decreased the acute phase and inflammatory in the formalin test. Moreover, STASP antinociceptive effect seems to be dose-dependent. RTASP and STASP do not have antinociceptive effect on the thermal stimuli evoked by the tail-flick apparatus. Other studies were needed to determine the mechanism of action of these molecules, however we speculate that they might be inhibiting at least COX-pathway and having some interaction in the excitatory transmission as NMDA antagonists.

Disclosures: E. Ramirez-San Juan: None. **C. Campos-Rodriguez:** None. **I. Cumbres-Vargas:** None. **A. Pineda-Pineda:** None. **R.M. Aguilar-Sanchez:** None. **J.G. Trujillo-Ferrara:** None.

Poster

483. Pain Models: Pharmacology

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Topic: D.03. Somatosensation – Pain

Support: CIHR Grant FDN148413
QPRN

Title: Analgesic efficacy of highly selective and biologically stable neurotensin type 2 receptor (NTS2) analogs

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Abstract: Endogenous neurotensin and the chemically modified NT(8-13) analogs inhibit the nociceptive transmission by interacting with two class A G protein-coupled receptors, namely NTS1 and NTS2. However, the binding of NT to NTS1 not only induces analgesia but also results in hypotension and hypothermia, which may represent barriers to adequate pain management. As opposed to NTS1, there is now substantial evidence indicating that NTS2-selective agonists may mediate analgesia without exerting changes in blood pressure or body temperature. Here, our goal was thus to design and characterize novel NT(8-13) analogs exhibiting high affinity and selectivity toward NTS2. To this aim, we synthesized a series of NT(8-13) analogs harboring site-specifically modified unnatural amino acids and reduced amide bonds. To target preferentially NTS2, Tyr^{11} was replaced by a *N-Homo*-Tyrosine (*N-h*Tyr) or by a *N-Homo*-Tryptophane (*N-h*Trp). Then, Pro^{10} and Leu^{13} were respectively substituted by the non-natural silylated amino acids, silaproline (Sip) and (trimethylsilyl)alanine (TMSAla).

Finally, a reduced amide bond (Ψ[CH_2NH]) was incorporated between the two Lys^8-Lys^9 residues to minimize peptide degradation. Our binding data revealed that these NT(8-13) analogs, codenamed JMV5297 (H-Lys-Ψ[CH_2NH]Lys-Pro-*N*-*h*Tyr-Ile-TMSAla-OH), JMV5298 (H-Lys-Ψ[CH_2NH]Lys-Sip-*N*-*h*Tyr-Ile-TMSAla-OH) and JMV5335 (H-Lys-Ψ[CH_2NH]Lys-Pro-*N*-*h*Trp-Ile-TMSAla-OH) showed good affinity for NTS2 (IC_{50}: 9.5 ± 2.1 nM; 11.9 ± 3.4 nM and 1.31 ± 0.17 nM, respectively) without binding activity at NTS1 (IC_{50}: > 20 µM for all analogs tested). In addition, these analogs were much more stable in plasma with half-lives exceeding 24 hours. Then, JMV5297 and JMV5335 were tested *in vivo* in acute (tail-flick test) and tonic (formalin test) pain models. We found that intrathecal (i.t.) injection of these two compounds at 90 µg/kg produced a significant analgesic response compared to saline-treated rats. At this dose, both compounds were also effective in reversing the nociceptive behaviors induced by intraplantar formalin. Importantly, both JMV5297 and JMV5335 did not produce hypothermia at the effective analgesic dose and did not induce hypotension after intravenous delivery. In conclusion, targeting the NTS2 receptor with selective NT analogs represents a promising alternative to opioids for pain management.

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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.25/J46

Topic: D.03. Somatosensation – Pain

Title: A transgenic model with humanized TRPA1 pore domain enables study of human-selective TRPA1 inhibitors in the rat

Authors: M. DOURADO[1], K. L. STARK[2], R. M. REESE[4], P. KARILA[5], S. LARDELL[5], K. ANDERSON[3], S. WARMING[3], *D. H. HACKOS[1];
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Abstract: Aim of investigation: The TRPA1 channel has been studied as a target for pain as well as respiratory conditions such as asthma. As such, the pharmaceutical industry has identified many small-molecule selective inhibitors of TRPA1 with the aim of testing these in clinical trials. Unfortunately, many otherwise potent drug-like TRPA1 inhibitors bind poorly to rodent TRPA1 channels due to amino acid differences in the binding site region within the pore domain. To enable pre-clinical testing of such compounds, we have developed a mutant rat model that fully humanizes the pharmacology of this binding site region.

Methods: Using CRISPR technology, we first developed a humanized TRPA1 rat where the entire human cDNA was inserted at the rat TRPA1 start site. Unfortunately, this led to a hypomorph with severely-reduced TRPA1 expression. We then constructed a mutant rat where we replaced only 10 amino acid residues that fully humanizes the small-molecule binding site within the pore domain. We used expression analysis, calcium imaging, high throughput calcium fluorimetry, and behavioral analysis to determine whether the expected humanized pharmacology was properly installed in this animal model.
Results: We found that our novel humanized binding-site knockin (KI) rat showed active functional expression of TRPA1 in DRG neurons with the expected cell body size distribution. Furthermore, these rats showed normal behavioral responses to AITC when applied to the hind paw, which is known to be TRPA1-dependent. Calcium fluorimetry experiments demonstrate that the expected humanized pharmacology is present in DRG neurons in culture. Finally, we show that AITC-induced behavioral responses can be blocked by a human-selective TRPA1 inhibitor.
Conclusions: Here we demonstrate a novel humanized rat model that allows pre-clinical testing of human-selective TRPA1 inhibitors. Our hope is that this model will facilitate the clinical development multiple classes of human-specific TRPA1 inhibitors.
Acknowledgements / Disclosures: MD, KS, RR, KA, SW, and DDH are employees of Genentech, Inc. SL and PK are employees of Cellectricon AB.

Disclosures: **D.H. Hackos:** A. Employment/Salary (full or part-time):; Genentech, Inc. **M. Dourado:** A. Employment/Salary (full or part-time):; Genentech, Inc. **K.L. Stark:** A. Employment/Salary (full or part-time):; Genentech, Inc. **R.M. Reese:** A. Employment/Salary (full or part-time):; Genentech, Inc. **K. Anderson:** A. Employment/Salary (full or part-time):; Genentech, Inc. **P. Karila:** A. Employment/Salary (full or part-time):; Cellectricon AB. **S. Lardell:** A. Employment/Salary (full or part-time):; Cellectricon AB. **S. Warming:** A. Employment/Salary (full or part-time):; Genentech, Inc..

Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.26/K1

Topic: D.03. Somatosensation – Pain

Support: Conacyt Grant 252702

Title: Pharmacological effect of hydrogen sulfide on the hypersensitivity to pain in male Wistar rats with insulin resistance

Authors: *J. H. BELTRÁN-ORNELAS, D. CENTURIÓN, D. L. SILVA-VELASCO, A. SÁNCHEZ-LÓPEZ, F. J. LÓPEZ-MUÑOZ;
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Abstract: Several lines of evidence have shown the potential role of hydrogen sulfide (H_2S) in insulin resistance and pain. However, up to date, the effect of H_2S in the hypersensitivity to pain during fructose-induced insulin resistance has not been evaluated. Thus, the aim of this study was to determine the effect of NaHS (sodium hydrosulfide; H_2S donor), DL-propargylglicine (DL-PAG; cystathionine-Ɣ-lyase inhibitor) and hydroxylamine (AOOA; cystathionine-β-synthase inhibitor) on the allodynia and hyperalgesia. For this purpose, 48 rats were divided into two groups. The first group (n=40) was treated with fructose (15% in drinking water) during 20 weeks, while the second group (control; n=8) received tap water. 16 weeks after the treatment with fructose, the first group was divided into 5 subgroups (n=8 each), which received daily i.p. administration during 4 weeks with: (1) nothing; (2) phosphate buffer saline (PBS; 1 ml/kg); (3) NaHS (5.6 mg/kg); (4) DL-PAG (10 mg/kg); and (5) AOOA (10 mg/kg). Next, oral glucose tolerance test and insulin levels were determined before and after administration of glucose (2 g/kg, p.o.). The rats were placed in acrylic cages on top of a wire mesh grid that allowed their paws access to the von Frey filaments. Bending forces of 8 and 60 g to the mid-plantar skin of right hind paw were applied. The filament was placed on the skin until it bowed slightly, each filament was presented ten times at a rate of about 1 second. A response was recorded if the rat withdrew its hind paw from the filament. Responses were converted into a frequency percent (%=number of responses/10 × 100). Animals treated with fructose showed hyperinsulinemia and insulin resistance. Interestingly, fructose-induced insulin resistance was reverted by AOOA and DL-PAG but not by PBS. NaHS only diminished the glucose basal and HOMA index. Control rats rarely withdrew its paw from 8 g stimuli and usually withdrew its paw from 60 g stimuli. Chronic treatment with fructose during 20 weeks: (1) presented response with 8 g stimuli, which indicates tactile allodynia, and (2) increased level of response seen with
60 g stimuli which indicates tactile hyperalgesia. Chronic treatment with NaHS did not modify the tactile allodynia and hyperalgesia. However, AOOA and DL-PAG reverted both tactile allodynia and hyperalgesia induced by insulin resistance. These data suggest that endogenous H_2S could be implicated in the pathophysiology of the insulin resistance and in the development alterations in nociception during this metabolic state.
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Poster

483. Pain Models: Pharmacology

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 483.27/K2

Topic: D.04. Somatosensation – Touch

Title: Evaluation of the antinociceptive effect of Ipomoea stans

Authors: *O. A. JARAMILLO-MORALES[1], C. A. MENDOZA-GÓMEZ[2], M. BAUTISTA-ÁVILA[2], C. VELÁZQUEZ-GONZÁLEZ[2], L. A. MORENO-ROCHA[3], M. SÁNCHEZ-ZAVALA[4], M. DE LA O-ARCINIEGA[2];
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Abstract: Ipomoea stans belongs to the convolvulaceae family, it is commonly known as "tumbavaquero" or "campanita". It is used in traditional medicine for muscular and visceral pains, epileptic attacks, as well as to calm the nerves, however, there is no scientific evidence to corroborate its analgesic effect, in this sense **the objective** of the present study was to evaluate the antinociceptive effect of the methanolic extract of *Ipomoea stans* in a nociceptive pain model in CD1 mice. **Methods**. The vegetal material was collected in the municipality of Mineral de la Reforma, State of Hidalgo, Mexico. The methanolic extract of *I. stans* was obtained by maceration of the aerial part (stem and leaves). The antinociceptive activity was evaluated using the Writhing model. **Results**. The intragastric administration of *I. stans* (300 mg/kg) showed effects in the temporal course, observing the maximum effect at 15 min post-administration. This effect was maintained over time, almost constantly during the 30 min. When evaluating the overall effect of antinociception, it was shown that *I. stans* had a similar effect to indomethacin. **Conclusion**. Our results indicate for the first time the antinociceptive activity of *I. stans* in a visceral pain, therefore this study contributes in part to the validation of the use of the species *I.stans* in traditional medicine with analgesic effect.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

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Program #/Poster #: 484.01/K3

Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01AA025996
NIH/NIAAA Institutional Research Training Grant T32AA007577

Title: Differential effects of opioid versus alcohol dependence on pain avoidance behavior and regional endocannabinoid system deficiency

Authors: *J. A. CUCINELLO[1], M. E. BERNER[2], A. R. PAHNG[1], K. N. EDWARDS[1], S. EDWARDS[1];
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Abstract: In contrast to their analgesic effects, chronic use of either opioids or alcohol produces the paradoxical emergence of a heightened state of pain sensitivity, termed hyperalgesia, during withdrawal. A hallmark symptom of hyperalgesia is the development of motivational strategies to avoid painful stimuli, and our lab has shown that adult male Wistar rats will display pain avoidance behavior using the mechanical conflict avoidance system during withdrawal from morphine (n=10-11/group) or alcohol (n=8-9/group). The present study sought to identify how morphine and alcohol differentially affect pain avoidance behavior and endocannabinoid signaling within pain- and avoidance- associated brain regions, including the periaqueductal grey (PAG) and basolateral amygdala (BLA). Western blotting was conducted for protein quantification of endocannabinoid system-related proteins cannabinoid receptor type 1 (CB_1R), diacylglycerol lipase alpha (DAGL*a*), monoacylglycerol lipase (MAGL), and fatty acid amide hydrolase (FAAH). We found that morphine and alcohol dependence produced distinct patterns of pain avoidance behavior, where morphine dependence produced more hyperalgesic behavior and ethanol dependence produced more allodynic behavior. Morphine dependence appears to cause hyperalgesia through deficient PAG endocannabinoid signaling, with pain avoidance behavior negatively correlating with PAG CB_1R levels across both saline- and morphine- treated groups. We also found that alcohol dependence may facilitate allodynic behavior through a similar dysregulation of endocannabinoid signaling within the BLA, were pain avoidance was negatively correlated with the ratio of BLA DAGL*a*:MAGL. Overall, we found evidence that endocannabinoid deficiency within the PAG and BLA is associated with increases in pain avoidance behavior in dependent animals, suggesting that exogenous cannabinoid treatment may be an effective therapy for substance-induced hyperalgesia.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: D.03. Somatosensation – Pain

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Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB32010200)
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Title: Different mechanisms mediate endogenous and exogenous opioid analgesia in inflammatory pain

Authors: *Y. DOU[1], X. ZHANG[1], M. ZHAO[2], Q. LI[1], A. LI[2], Y. SUN[1];
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Abstract: Mu-opioid receptors (MORs) are widely expressed in the central nervous system and are crucial for opioids analgesia. However, the functional role of the MORs expressed in different types of neurons in opioid analgesia still remains largely unknown. Here, we demonstrated that distinct neuronal populations mediate analgesic effects of exogenous and endogenous opioids on inflammatory pain. We took advantage of the fluorescence micro-optical sectioning tomography (fMOST) serial technology to provide a global view of the distribution of MOR^+ neurons in the brains. Using of a new genetic mouse model, we selectively expressed MORs in different subsets of neurons and examined their roles in opioid analgesia. We found that morphine-induced analgesia of both acute and chronic inflammatory pain is mediated by MORs in glutamatergic but not GABAergic neurons. In contrast, the analgesic effect of endogenous opioids on inflammatory pain is mediated by MORs in GABAergic neurons but not glutamatergic neurons. Thus, our study demonstrated that the MORs expressed in excitatory and inhibitory neurons are differentially involved in exogenous and endogenous opioid analgesia.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.03/K5

Topic: D.03. Somatosensation – Pain

Title: Effect of protein kinase C inhibition within the periaqueductal gray on morphine antinociceptive tolerance

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Abstract: The ventrolateral periaqueductal gray (vlPAG) is an important midbrain region that regulates the descending pain modulatory system and is implicated in the development of antinociceptive tolerance to opioid analgesics. Protein Kinase-C (PKC) is a Ser/Thr kinase that phosphorylates the μ-opioid receptor (MOPr) following morphine agonism. This phosphorylation is responsible for desensitization of the receptor, resulting in the termination of G-Protein signaling. It is speculated that PKC-mediated desensitization of the MOPr does not readily lead to the internalization of the receptor, thus contributing to tolerance. Previous studies have shown that intracerebroventricular administration of PKC inhibitors prevented the development of morphine tolerance in mice. Further, a non-specific PKC/GRK inhibitor was able to block the development of morphine tolerance in the vlPAG. However, the contribution of PKC to morphine tolerance in the vlPAG has not been directly explored. Using immunofluorescence staining, we observed increased phosphorylated PKC that is co-localized with the MOPr at the cell membrane of vlPAG neurons in morphine-tolerant animals. Further, we assessed the development of morphine antinociceptive tolerance following pre-treatment with the PKC inhibitor, Gö-7874, which targets conventional PKC isoforms. The compound was bilaterally microinjected into the vlPAG of wild-type mice prior to the commencement of a chronic morphine tolerance paradigm. The analgesic effects of morphine were assessed using Hot Plate and Tail Flick tests, which are respectively representative of supra-spinal and spinal thermal nociceptive responses. This study contributes to the understanding of PKC-mediated MOPr desensitization processes leading up to morphine tolerance.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: D.03. Somatosensation – Pain

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Advanced Brain Research International, Inc. (CH28045)
Nakatomi Foundation.

Title: Neuropeptide oxytocin enhances μ opioid receptor signaling as a positive allosteric modulator

Authors: *Y. MEGURO[1,2], K. MIYANO[2], S. HIRAYAMA[3], H. FUJII[3], Y. UETA[4], N. SATA[1], T. YADA[5,6], Y. UEZONO[2,7];
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Abstract: Oxytocin (OT) is a 9-amine neuropeptide that plays an essential role in mammalian labor, lactation, maternal bonding, and social affiliation. OT has been reported to exert an analgesic effect in both humans and animals, and the results of certain animal experiments have shown that the analgesic effect of OT is partially blocked by opioid receptor antagonists. To investigate the relationship between OT and μ opioid receptor (MOR), we evaluated how OT affects MOR in vitro by performing an electrical impedance-based receptor biosensor assay (CellKey™ assay), an intracellular cAMP assay, and a competitive receptor- binding analysis by using cells stably expressing human MOR and OT receptor. In both the CellKey™ assay and the intracellular cAMP assay, OT alone exerted no direct agonistic effect on human MOR, but treatment with 10^{-6} M OT markedly enhanced the MOR signaling induced by 10^{-6} M endomorphin-1, β- endorphin, morphine, fentanyl, and DAMGO. Moreover, in the competitive receptor-binding assay, 10^{-6} M OT did not alter the affinity of endomorphin-1 or morphine for MOR. These results suggest that OT could function as a positive allosteric modulator that

regulates the efficacy of MOR signaling, and thus OT might represent a previously unrecognized candidate analgesic agent.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

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Program #/Poster #: 484.05/K7

Topic: D.03. Somatosensation – Pain

Support: NIH/NIDCR R01 DE025393-01A1

Title: OPRM1 transfection reduces nociception and mortality in oral cancer mouse models

Authors: ***N. H. TU**, K. INOUE, H. WILLIAM, M. S. AHMAD, R. X. DANG, H. D. TRAN, D. H. KIM, E. DOWSE, I. KENTARO, S. YAMANO, B. L. SCHMIDT;
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Abstract: Oral squamous cell carcinoma (SCC) is debilitating and painful. Novel treatment for oral cancer pain is needed. We previously showed that the mu-opioid receptor is downregulated in human oral cancer patients due to OPRM1 methylation. Upregulation of OPRM1 via viral-mediated gene transfection shows promise for analgesic treatment. However, there are safety concerns associated with viral vectors including a strong immune response and cytotoxicity. To overcome these concerns, we developed a non-viral hybrid vector: HIV-1 Tat peptide sequence modified with histidine and cysteine residues combined with a cationic lipid. We utilized a mouse oral cancer model induced through 16 weeks of exposure to 4-Nitroquinoline 1-oxide (4NQO) in the drinking water. After tongue cancer developed, we quantified gnawing activity in a dolognawmeter. Extended gnaw-time in the dolognawmeter was used as a behavioral index of oral nociception. We transfected OPRM1 with our non-viral vector once mouse gnaw-time in the dolognawmeter was statistically longer in duration than baseline values for each mouse. OPRM1 transfection significantly reduced gnaw-time at post-transfection day 8 (73.8 ± 73.7 vs 94.3 ± 71.2), 16 (27.7 ± 44.0 vs 112.4 ± 66.2) and 24 (47.2 ± 25.7 vs 114.7 ± 81.2). We infer from these results that OPRM1 transfection reduced nociception secondary to oral SCC. Additionally, OPRM1 transfection increased the survival rate compared to control mice at day 24 (100% vs 44.4%). Furthermore, the transfected mice showed no signs of systemic inflammation.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.06/K8

Topic: D.03. Somatosensation – Pain

Title: Daily intermittent fasting in mice enhances morphine induced anti-nociception while mitigating multiple side effects

Authors: *D. I. DURON, J. M. STREICHER;
Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: The opioid epidemic has continued to plague the United States with high levels of abuse and poor quality of life for chronic pain patients requiring continuous use of opioids. Many potential solutions have been proposed to mitigate this epidemic including new medications to reduce the abuse and side effect profiles of opioids; however, new medications are plagued by low efficacy, abuse potential, and toxicities. These limitations suggest that non-pharmacological interventions could be more efficacious with low side effect profiles. Intermittent fasting (IF) is a time restriction diet which has recently grown in popularity over the past decade in the prevention and mitigation of a variety of pathological states. Numerous animal and human studies have shown the benefits of IF in these disease states, but not in opioid treatment paradigms. We thus subjected male and female CD1 mice to 18-hour fasting intervals followed by 6-hour feed periods with standard chow for 1 week. Mice which underwent this diet displayed an enhanced anti-nociceptive response to systemic morphine both in efficacy and duration using thermal tail flick and post-operative paw incision pain models. While showing enhanced anti-nociception, IF mice also demonstrated a reduction in the development of anti-nociceptive tolerance using the thermal tail flick assay paired with daily systemic morphine treatment. We also found a reduction in the development of opioid induced constipation using both fecal mass and fecal pellet count in IF mice. Seeking a mechanism for our behavioral findings, we performed ^{35}S-GTPγS assays to assess the functionality of mu opioid receptors within the spinal cord and periaqueductal grey (PAG) tissues from IF mice with and without chronic morphine treatment. The resulting DAMGO concentration-response curves demonstrated an increased efficacy of mu opioid receptors within the spinal cord in IF mice and an absence of the development of tolerance within the PAG in IF mice, suggesting site-specific receptor mechanisms for the behavioral effects we observed. These data suggest that a daily IF diet may improve the therapeutic index of acute and chronic opioid therapies for pain patients in the clinic, both in improved analgesia and reduced tolerance and constipation.

Disclosures: D.I. Duron: None. **J.M. Streicher:** None.

Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.07/K9

Topic: D.03. Somatosensation – Pain

Support: MRC 2013918

Title: Kappa opioid receptors mediate TRPA1 analgesia

Authors: *E. SEMIZOGLOU, C. GENTRY, S. BEVAN, D. A. ANDERSSON;
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Abstract: The available therapies for chronic pain fail to provide permanent relief to patients and are often associated with severe side effects. Chronic pain has led to over-prescription of opioid analgesics and has contributed to the increasing rates of opioid addiction and deaths. The need for novel analgesics devoid of side effects in the central nervous system is therefore urgent. The aim of this study is to explore the modulation of nociception, mediated by a crosstalk of opioid receptors and TRP (Transient Receptor Potential) channels in the peripheral nervous system.Transgenic mice lacking TRPA1 (Transient Receptor Potential Ankyrin 1) have reduced sensitivity to mechanical stimulation. We discovered that this sensory loss is related to peripheral KOR (Kappa Opioid Receptors) which are engaged in the absence of TRPA1. Administration of KOR antagonist normalizes this phenotype in *Trpa1*$^{-/-}$ mice but has no effect on nociception in wild type mice. *In vivo* calcium imaging experiments of the L4 DRGs (Dorsal Root Ganglia) reveal that less neurons respond to mechanical stimulation in *Trpa1*$^{-/-}$ mice, compared to wild type. This sensory abnormality is reversed by administration of the opioid receptor antagonist naloxone but not by saline. *In situ* hybridization experiments in lumbar DRGs from wild type mice show that approximately 40% of the KOR positive neurons also express *Trpa1*. Transcriptomic and protein levels of KOR in DRGs from wild type and *Trpa1*$^{-/-}$ mice are unaltered according to RNA sequencing, qPCR, western blot and ELISA assays. We are currently studying the interactions between KOR and TRPA1 in HEK293 cells. To conclude, the sensory deficits of *Trpa1*$^{-/-}$ mice are not directly related to the loss of TRPA1 but are explained by increased activity of KOR in the periphery. Ongoing studies will identify the molecular mechanisms for TRPA1 modulation of KOR activity. Our results may facilitate identification of molecular targets for new analgesic therapies for chronic pain.

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Poster

484. Somatosensation: Pain and Opioids

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Topic: D.03. Somatosensation – Pain

Support: Craig H. Neilsen Foundation (Award #213959)

Title: A role for dopaminergic signaling in opioid resistance following spinal cord injury

Authors: *H. M. RODGERS, R. PATTON, J. YOW, S.-A. LIM, S. CLEMENS, K. L. BREWER;
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Abstract: Opioids are not universally effective in treating neuropathic pain following spinal cord injury (SCI). We have shown in a rat model of SCI that 2/3 of the animals do not respond to morphine, but adjuvant addition of a dopamine (DA) D1R antagonist or D3R agonist was able to restore the lost morphine response, suggesting that morphine resistance after SCI involves DA-ergic signaling. The aim of this study was to determine the analgesic response of morphine-responsive and nonresponsive SCI rats to DA modulators alone and in combination with morphine and determine if changes in CNS DA levels were associated with the altered morphine response. Baseline nociceptive thresholds were measured in uninjured (n = 8) and SCI (n = 25) adult female rats before and after injection of morphine (2mg/kg) or saline (control). Rats then had thresholds re-assessed after injection of morphine + pramipexole (D3 agonist; 0.1mg/kg), morphine + SCH 39166 (D1 antagonist; 0.1mg/kg), pramipexole, or SCH 39166. Lumbar spinal cord and striatum samples were collected from a subset of rats in all groups and processed for metabolomics and targeted mass spectrometry to identify metabolite differences and quantify levels of DA. Morphine alone increased sensory thresholds in all uninjured rats but only 1/3 of SCI rats responded to morphine. SCI animals, regardless of response to morphine, showed improved analgesia with morphine + D3R agonist. However, only SCI nonresponsive rats showed improved analgesia with morphine + D1R antagonist compared to morphine alone. Metabolomics principal component analysis identified three clusters that corresponded to uninjured, SCI morphine-responsive and SCI morphine-nonresponsive groups. Preliminary analysis suggests differences in DA, prostaglandin and endogenous opioids pathways. Striatal DA levels were decreased in SCI morphine-nonresponsive rats compared to SCI morphine-responsive animals. In the lumbar spinal cord, DA levels were decreased in both morphine-responsive and nonresponsive SCI rats compared to uninjured rats. These data suggest that differences in DA pathways may affect morphine responsiveness following SCI.

Disclosures: H.M. Rodgers: None. **R. Patton:** None. **J. Yow:** None. **S. Lim:** None. **S. Clemens:** None. **K.L. Brewer:** None.

Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.09/K11

Topic: D.03. Somatosensation – Pain

Support: NIH Grant R21 DA040305 (DS)
NIDDK Intramural Research Program Z01 DK031117-26 (KAJ)

Title: A_3 adenosine receptor activation prevents opioid-induced hyperalgesia and antinociceptive tolerance

Authors: *T. M. DOYLE[1], T. M. LARGENT-MILNES[2], E. ESPOSITO[3], V. STAIKOPOULOS[4], Z. CHEN[1], R. DALGARNO[5], M. MOUSSEAU[5], D. TOSH[6], S. CUZZOCREA[3], K. A. JACOBSON[6], T. TRANG[5], M. HUTCHINSON[4], G. J. BENNETT[7], T. VANDERAH[2], D. SALVEMINI[1];
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Abstract: Effective opioid therapies to treat chronic pain are compromised by several inter-related drug-induced phenomena, such as opioid-induced hyperalgesia (OIH), antinociceptive tolerance and withdrawal. Novel opioid-sparing approaches are needed as the broad use of opioids and rates of opioid-related addiction and mortality have risen to constitute the current ”opioid epidemic.” However, the underlying mechanisms of OIH, antinociceptive tolerance and withdrawal remain poorly understood. We identified a novel mechanism whereby sustained opioid administration drives OIH and tolerance through adenosine kinase (ADK)-dependent dysregulation of adenosine signaling at the A_3 adenosine receptor (A_3AR). Subcutaneous infusion of morphine in rodents led to the development of OIH and tolerance that was associated with increased expression of adenosine kinase (ADK; the major enzyme determinant of extracellular adenosine concentrations) in the dorsal horn of the spinal cord. Intrathecal administration of the ADK inhibitor, ABT-702, attenuated the development of OIH and tolerance and these beneficial effects were lost when A_3AR was blocked with intrathecal administration of the A3AR antagonist, MRS1523. This suggests that A_3AR activation counter-regulates the adverse effects of morphine. Indeed, administration of A_3AR agonists (IB-MECA, MRS5698 or MRS5980) prevented the development of OIH and tolerance. Moreover, A_3AR agonists also reduced naloxone-precipitated withdrawal behaviors. At the molecular level, A_3AR agonists inhibited NLRP3 inflammasome activation and expression of the neuroexcitatory and

inflammatory cytokine, interleukin-1β. Our results demonstrate that the loss of adenosine/A_3AR signaling is critical to the development of opioid-induced adverse effects and provide the pharmacological rationale to support clinical evaluation of A_3AR agonists as adjunct therapy to opioids.

Disclosures: **T.M. Doyle:** None. **T.M. Largent-Milnes:** None. **V. Staikopoulos:** None. **S. Cuzzocrea:** None. **K.A. Jacobson:** None. **T. Trang:** None. **G.J. Bennett:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A founder of BioIntervene, Inc. that licensed related intellectual property from Saint Louis University and the National Institute of Health.. **Z. Chen:** None. **D. Salvemini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A founder of BioIntervene, Inc. which has licensed related intellectual property from Saint Louis University and the National Institute of Health.. **M. Hutchinson:** None. **E. Esposito:** None. **M. Mousseau:** None. **R. Dalgarno:** None. **D. Tosh:** None. **T. Vanderah:** None.

Poster

484. Somatosensation: Pain and Opioids

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.10/K12

Topic: D.03. Somatosensation – Pain

Support: NIDA Grant 2P50DA005010

Title: Effects of oxycodone on striatal direct and indirect pathway medium-sized spiny neurons in dorsal striatum

Authors: ***J. BARRY**[1], K. D. OIKONOMOU[1], E. DONZIS[1], S. CHOPRA[1], C. Y. YANG[3], P. GOLSHANI[3], C. J. EVANS[2], M. S. LEVINE[1], C. CEPEDA[1];
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Abstract: Opioids, in particular oxycodone, are currently the treatment of choice for severe pain. Opioid effects are mediated principally by the μ-opioid receptor (MOR) class of G protein-coupled receptors. MORs are abundant in various brain regions, including the ventral and dorsal striatum. However, little is known about potentially differential effects of opioids on direct and indirect pathway medium-sized spiny neurons (MSNs) in dorsal striatum. As the main effect of MOR activation is cell membrane hyperpolarization, we hypothesized that action potential firing and Ca^{2+} transient activity of MSNs would be reduced after oxycodone administration. To test this hypothesis, we combined viral expression of a genetically-encoded Ca^{2+} indicator, GCaMP6f with a miniaturized microscope (miniscope) to image spontaneous Ca^{2+} activity in

direct and indirect pathway MSNs of freely-moving mice before and after systemic injection of oxycodone (10 mg/kg) or control vehicle. D1- and A2A-Cre mice (aged 3-4 months) were injected with GCaMP6f and after 2 weeks the cortical tissue overlying the striatum was removed to allow implantation of a GRIN lens. 2-3 weeks later, a baseplate to hold the miniscope was affixed to the skull. Ca^{2+} activity was correlated with mouse behavior using a time-synced videocamera. Miniscope movies were analyzed using custom-written MATLAB scripts. In control conditions MSNs of the direct and indirect pathway displayed Ca^{2+} transients in close association with movement initiation and exploratory activity. Oxycodone injection induced typical MOR activation signs including hyperactivity, Straub tail, and gait disturbances. Interestingly, the number of MSNs displaying Ca^{2+} transients was reduced. Similarly, the amplitude and frequency of Ca^{2+} transients decreased after oxycodone. There also appeared to be a major dissociation between Ca^{2+} transient activity and behavior after oxycodone treatment as movements were no longer correlated with increased Ca^{2+} activity. Following imaging experiments, mice were used for slice electrophysiology to investigate the effects of oxycodone on GCaMP6f-expressing direct and indirect pathway MSNs. Whole-cell patch clamp recordings in current clamp mode indicated that bath application of oxycodone (10μM) induced cell membrane hyperpolarization and reduced the number of action potentials evoked by depolarizing current pulses. These results demonstrate that oxycodone reduces Ca^{2+} transient activity and favors membrane hyperpolarization as well as decreased firing regardless of MSN subtype. Findings also suggest that hyperactivity after opiates is mediated by a pathway other than the dorsal striatum.

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Poster

484. Somatosensation: Pain and Opioids

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Topic: D.03. Somatosensation – Pain

Support: Ministry of Science and Technology, Taiwan MOST 108-2321-B-002-005
Ministry of Science and Technology, Taiwan MOST107-2811-B-002-008
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Ministry of Science and Technology, Taiwan MOST106-2321-B-002-019
National Health Research Institutes, Taiwan NHRI-EX107-10733NI
Ministry of Education, Taiwan 107M4022-3

Title: Acupuncture attenuates neuropathic pain and opioid tolerance in mice via orexin-initiated endocannabinoid signaling in the periaqueductal gray

Authors: *M.-T. LEE[1,2], L.-C. CHIOU[1,2,3];
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Abstract: Opioids are indispensable in pain management, but their long-term efficacy in suppressing chronic pain is hindered by the development of tolerance. Clinically, opioid tolerance can be delayed by co-administration of non-opioid analgesics. We have recently revealed a nondrug, non-opioid analgesic mechanism induced by electroacupuncture at the PC6 (Neiguan) acupoint (EA-PC6), which overlays the median nerve, in mice.[1] Briefly, EA-PC6 at low frequency (2 Hz, 2 mA, 0.15 ms) can trigger orexin release from the lateral hypothalamus into the ventrolateral periaqueductal gray (vlPAG), a midbrain region for initiating descending pain inhibition. Orexin then activates postsynaptic orexin 1 receptors (OX1Rs), a Gq protein-coupled receptor family, in the vlPAG, resulting in synthesis of 2-arachydonoylglycerol (2-AG), an endocannabinoid that produces retrograde inhibition of GABA release by activating presynaptic cannabinoid 1 receptors (CB1Rs), leading to disinhibition of the vlPAG, and ultimately inducing analgesia. Here, we further examined whether repeated administrations of EA-PC6 can attenuate chronic pain without developing tolerance, and prevent the development of opioid tolerance in mice with neuropathic pain induced by chronic constriction injury (CCI) at the right sciatic nerve. The CCI-mice were left to develop neuropathic pain for 7 days. Their allodynia responses of were evaluated by the paw-withdrawal threshold to the von Frey filaments. From day8 to day14, CCI-mice were daily treated with morphine (10 mg/kg, *i.p.*), EA-PC6 or morphine+EA-PC6. We found that repeated treatments with EA-PC6 significantly suppressed mechanical allodynia in CCI-mice. However, repeated EA-PC6-induced analgesia (rEA-PC6-IA) did not develop tolerance as compared with repeated treatment of morphine for 7 days, and opioid tolerance (OT) in these mice were reversed by EA-PC6. Moreover, EA-PC6 co-administered with daily morphine injection significantly prevented the development of OT, for 7 days. Mechanistically, the OT-reversal and OT-preventive effects of EA-PC6 were prevented by either SB334867 (an OX1R antagonist, 15 mg/kg, *i.p.*) or AM251 (a CB1R antagonist, 1.1 mg/kg, *i.p.*), suggesting the involvement of OX1Rs and CB1Rs. These results suggest that EA-PC6 can either reverse or prevent OT via the disinhibition mechanism mediated by OX1R-initiated endocannabinoid-CB1R signaling in the vlPAG. Thus, EA-PC6 is a potential novel pain management strategy in OT-inflicted patients, such as terminal cancer patients. [1]Chen YH, Lee HJ, Lee MT, et al. (2018) Proc Natl Acad Sci USA. 115(45):E10720.

Disclosures: **M. Lee:** None. **L. Chiou:** None.

Poster

484. Somatosensation: Pain and Opioids

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.12/K14

Topic: D.03. Somatosensation – Pain

Support: State of Washington Initiative Measure No. 171

Title: Effect of hyperbaric oxygen (HBO_2) on withdrawal-induced hyperalgesia during spontaneous withdrawal in morphine-dependent mice

Authors: *A. L. BREWER[1], D. Y. SHIRACHI[2], R. M. QUOCK[1];
[1]Psychology, Washington State Univ., Pullman, WA; [2]Physiol. and Pharmacol., Univ. of the Pacific, Stockton, CA

Abstract: With the opioid epidemic showing few signs of abating, new strategies for treating both pain and opioid dependence are needed. Hyperalgesia occurs as a result of opioid withdrawal and plays a role in relapse [Carcoba et al., *J Addict Dis 30(3): 258-70,* 2012]. Hyperbaric oxygen (HBO_2) is 100% oxygen administered at higher-than-atmospheric pressure. HBO_2 has shown promise in reducing pain in both preclinical animal models and in clinical conditions [Gibbons at al., *Brain Res. 1537:111-6,* 2013; Zhang et al., *Brain Res. 1711:41-*4, 2019; Efrati et al., *PLOS One 10(5)1-25,* 2015]. Furthermore, HBO_2 effectively reduced somatic signs of opioid withdrawal in animal models [Nicoara et al., *Brain Res. 1648:434-7,* 2016]. Collectively, these results indicate that HBO_2 may be effective for reducing hyperalgesia associated with opioid withdrawal. We assessed the effect of HBO_2 treatment on hyperalgesia in mice undergoing spontaneous withdrawal. Male and female NIH Swiss mice were made dependent upon morphine by twice daily *s.c.* injections of escalating doses of morphine for 4 consecutive days (50-125 mg/kg morphine). Following a final injection of morphine on Day 5, morphine injections ceased. Mice were treated with either HBO_2 or room air (RA) using two different treatment designs. The first treatment design featured a single 30-min treatment of 3.5 atmospheres absolute (ATA) HBO_2 or RA 60 min prior to hyperalgesia assessment at 10 h after the last morphine injection. The second treatment design consisted of multiple treatments of 2.5 ATA HBO_2 or RA prior to the 11, 25, 35, 49, and 59 h time points. Hyperalgesia was assessed by taking paw withdrawal thresholds to increasing paw pressures were recorded prior to the first injection and at 5, 10, 24, 34, 48, 58, 72, 82, 96 and 106 h after the final injection for one set of experiments (single high pressure exposure) and at 5, 11, 25, 35, 49, 59, 72 and 82 h for the second set of experiments (multiple lower pressure exposures). Both treatment paradigms effectively reduced hyperalgesia during withdrawal in both male and female mice. This data indicates that HBO_2 may be an effective way to treat hyperalgesia associated with opioid withdrawal.

Disclosures: **A.L. Brewer:** None. **R.M. Quock:** None. **D.Y. Shirachi:** None.

Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.13/K15

Topic: D.03. Somatosensation – Pain

Title: Chinese herbal extract attenuates morphine tolerance and dependence

Authors: *K. NUSEIR[1], I. MARMOUZI[2], A. ALACHKAR[3], O. CIVELLI[4];
[1]Jordan Univ. of Sci. and Technol., Irbid, Jordan; [2]Univ. of California at Irvine, Irvine, CA; [3]Pharmacol., [4]Univ. of California Irvine, Irvine, CA

Abstract: The opioid epidemic is a global problem that attracted the attention of authorities worldwide. In order to solve this problem, research had focused on finding alternatives. Unfortunately, until now, there are no better replacements for opioids; which still is the gold standard when it comes to analgesia. Traditional herbal medicine has been rising in popularity; and traditional Chinese medicine (TCM) gained most recognition globally. One of these TCM is an extract (YHS) of a plant traditionally used to treat pain and inflammation for thousands of years in China. The combination of opioids and herbal medicine for the treatment of pain is not highly explored. In order to examine the outcome of combining YHS with opioids on acute and inflammatory pain, we are proposing experiments to evaluate this effect. Morphine with YHS in varying concentrations will be administered to mice and acute as well as inflammatory pain responses will be measured using well-established models of pain. In addition, the combinations of YHS and morphine given to mice over a long term (1 week) in order to study tolerance and addiction development. Results of this study will supplement our knowledge about opioids and their use to treat pain. Furthermore, results of this study will elucidate more regarding tolerance to opioids. Most importantly, results of this study might bring us one-step closer to combat the opioid epidemic.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.14/K16

Topic: D.03. Somatosensation – Pain

Support: NIH F31 DA046122

Title: Upregulation of the μ-opioid receptor in response to naltrexone occurs via an endoplasmic reticulum exit site-dependent pathway

Authors: *S. GRANT[1], A. K. MUTHUSAMY[1], H. A. LESTER[2];
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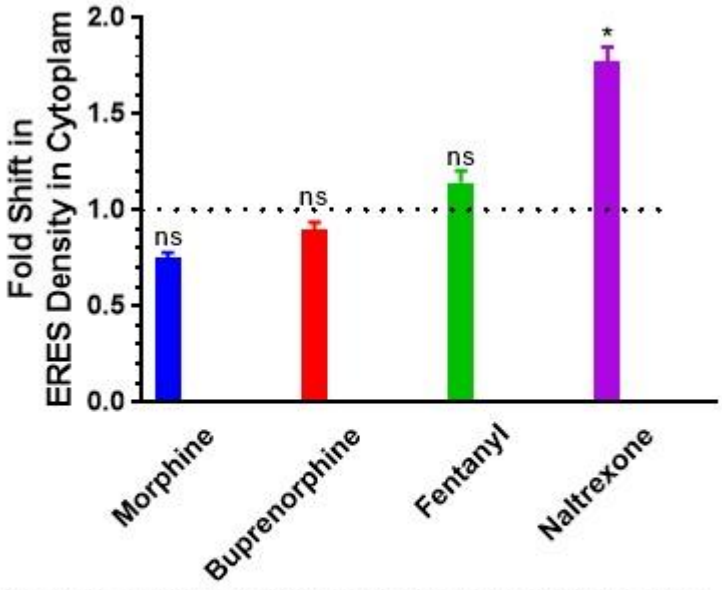

Figure 1. Changes in ERES density after opioid receptor ligand incubation. Each compound was used at 10 μM and incubated in the SH-SY5Y cell media for 12 h. Normalized to vehicle-treated cells (dotted-line). For each condition, n > 20 cells. Data are the mean ± S.E.M. *,p<0.05; ns, p>0.05 (unpaired t-test).

Abstract:

Understanding the mechanisms of μ-opioid receptor (MOR) sensitivity will be vital to fighting the global opioid epidemic. The most common opioid antagonists, naltrexone (Ntx) and naloxone, increase surface levels of MOR, causing individuals to become more sensitive to opioid agonists. Following antagonist treatment, any relapse to opioid agonist use presents a risk of overdose. In contrast, many opioid agonists, including fentanyl and the endogenously expressed MOR agonist peptides, decrease the levels of surface MOR protein. The mechanisms regulating MOR surface levels are incompletely known. We hypothesize that endoplasmic reticulum exit sites (ERES) participate early in the pathway of antagonist-induced upregulation of MOR surface levels, but not in agonist-induced downregulation. Using fluorescently tagged Sec24, a component of ERES, and super-resolution microscopy, we observe ERES in living SH-SY5Y cells. To describe details of cellular ERES levels, we take z-stacks using the Zeiss® Fast Airyscan module. In cells transfected with the ER-retained MOR N190K, we found that the

fraction of cytoplasm occupied by ERES increased after 12 hr incubation in 10 µM Ntx, but not in morphine, fentanyl, or buprenorphine (Figure 1). We also assessed whether ERES levels change with morphine and fentanyl using a MOR mutant that lacks the ability to become phosphorylated at S375 (a critical phosphorylation site for MOR function). We observed no differences in ERES levels under these conditions, suggesting that the lack of ERES change by agonists is not due to S375 phosphorylation. We also measured changes in cyclic adenosine monophosphate (cAMP) levels due to Ntx, to test the hypothesis that ERES levels change in response to cAMP levels. We show that Ntx does not change cAMP levels. These results support the hypothesis that the upregulation event proceeds via ERES while the downregulation event does not (agreeing with evidence that downregulation proceeds via endocytosis). These data suggest that Ntx is entering the cell, entering the ER, and serving as a pharmacological chaperone of the MOR.

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Poster

484. Somatosensation: Pain and Opioids

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Topic: D.03. Somatosensation – Pain

Support: VA Merit grant 1I01BX003451
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Title: Positive allosteric modulation of cannabinoid type-1 receptors (CB1R) attenuates the anti-hyperalgesic effects of a mu opioid receptor (MOR) agonist in theperiaqueductal gray (PAG) of morphine-withdrawn rats

Authors: *J. W. MIDDLETON[1], U. DATTA[3], L. K. KELLEY[2], T. D. LOBELL[2], N. W. GILPIN[4];
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Abstract: Chronic opioid drug use produces tolerance to the analgesic effects of opioids and cessation of opioid use can produce or exaggerate hyperalgesia. Cannabinoids are a potential alternative to opioids for the treatment of pain because they modulate pain in central pathways, and cannabinoid receptors (CBRs) are found in many of the same brain regions as opioid receptors. Nociception and pain are mediated by a complex set of circuits, and molecular and cellular brain processes. One critical site for pain modulation is the periaqueductal gray (PAG),

which receives ascending pain information and modulates pain via projects to the medulla. Activation of pre-synaptic mu-opioid receptors (MORs) in the PAG suppresses inhibitory synaptic transmission, thereby disinhibiting medulla-projecting neurons to promote anti-nociception. Positive allosteric modulators (PAMs) of CB1Rs modulate the functional effects of cannabinoid receptor activation; GAT211, a CB1R PAM, exhibits anti-nociceptive effects in animal models of chronic inflammatory pain. We used a combination of brain slice electrophysiology and behavioral pharmacology to test the interaction effects of GAT211 and the MOR agonist DAMGO on PAG synaptic transmission and thermal nociception in rats treated with chronic morphine and tested (or sacrificed) during withdrawal. Some rats were implanted with cannulae aimed at the PAG for four behavioral pharmacology experiments (GAT211 dose-response, DAMGO dose-response, DAMGO timecourse, and GAT211-DAMGO dual treatment). Separate rats were sacrificed after the 7thday of morphine treatment for cellular recordings in ventrolateral PAG brain slices. In the slice, GAT211 alone did not affect synaptic inhibition in vlPAG neurons, and GAT211 attenuated DAMGO-induced suppression of synaptic inhibition in the same neurons. *In vivo*, intra-PAG GAT211 treatment did not affect thermal nociception in morphine-treated rats or saline-treated controls. Intra-PAG DAMGO treatment produced robust dose-dependent anti-nociceptive effects in morphine-treated and saline-treated rats. Intra-PAG GAT211 treatment attenuated the anti-nociceptive effects of DAMGO in morphine-withdrawn rats, but did not alter DAMGO effects on thermal nociception in saline-treated controls. These findings support the conclusion that CB1R positive allosteric modulation antagonizes the cellular and behavioral effects of the MOR agonist DAMGO in the PAG. This suggests that opioid-sparing effects of cannabinoids may occur outside the PAG, and lays the foundation for future work on CB1R-MOR interaction effects in PAG microcircuits.

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Poster

484. Somatosensation: Pain and Opioids

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.16/K18

Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01 CA142115-07

Title: Chronic opioids and cannabinoids in models of chronic pain and pathologic bone fracture

Authors: *A. L. THOMPSON, H. CICCONE, D. MOHTY, A. SMITH, J. CONTRERAS, A. LANE, J. SORENSON, T. M. LARGENT-MILNES, T. W. VANDERAH;
Pharmacol., Univ. of Arizona, Tucson, AZ

Abstract: Fractures, both pathologic and traumatic, can result in severe chronic pain that leads to decreased quality of life and functional status. Opioids are a main therapy used to control bone pain but, have off target, detrimental effects on the bone itself. We explored the role of chronic opioids and cannabinoids in two models of murine fracture to assess their effects on bone health. In our cancer induced bone fracture model, female C57BL/6J mice (15-20g) underwent implantation of 80,000 breast adenocarcinoma cells (E0771) into the right femoral cavity. Sham operated animals underwent the same procedure, but were injected with cell media only. Spontaneous pain behaviors were measured by blinded observer, flinching and guarding, at baseline, 7, 10 and 14 days post-surgery. Morphine or saline was administered via osmotic minipump from days 7 to 14 post surgery. In our traumatic fracture model, C57BL/6J mice (15-25g) underwent femoral implantation of a stainless-steel pin into the right femoral cavity. A mid-diaphyseal fracture was initiated using a three-point bending device. Sham animals received the femoral pin alone. Spontaneous and evoked pain behaviors were taken at baseline, 1, 7, 14, 21 and 28 days post-fracture by a blinded observer. Ambulation measurements were also obtained at weekly intervals to assess activity. Animals were treated with morphine or cannabinoids from days 1-28 post fracture via minipump. Inflammatory cytokines (e.g. IL-1, IL-6, TNFalpha) were measured by quantitative PCR and ELISA, bone degradation was analyzed via radiographs and micro-computed tomography (μCT) and cell quantifications were done using flow cytometry. Opioid hyperalgesia and tolerance were observed in our models, while cannabinoids maintained their efficacy over the study. Significant changes in gene expression of inflammatory cytokines and bone metabolic regulators were observed in the bone tissue in animals chronically treated with morphine, with the cannabinoids modulating this change in gene expression. In addition, the animals treated with sustained morphine had accelerated bone loss as measured by both radiograph and μCT. Cannabinoid agonists helped mitigate morphine -induced bone loss. Chronic morphine administration modulated healing time and attenuated callus bridging. Cannabinoid compounds were effective in pain control and did not affect healing time of fracture. This suggests that chronic opioids have negative effects on bone in addition to their other deleterious side effects, while cannabinoids are worth investigating for pain control in bone disease due to their efficacy in pain management, as well as their potential benefits to bone healing.

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Poster

484. Somatosensation: Pain and Opioids

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Topic: D.03. Somatosensation – Pain

Support: National Natural Science Foundation of China (NFSC81320108012)
Natural Science Foundation of Beijing-Key Project (NSFB-7191001)

Title: Roles of Wnt signaling in physical dependence on morphine in mice

Authors: M. WU[1,2,3], Z.-H. LI[2], L. LIANG[2], P. MA[1], D. LIU[1], F. RAO[1], ***X.-J. SONG**[1,2]; [1]SUSTech Ctr. for Pain Med. and Med. Sch., Southern Univ. of Sci. and Technol., Shenzhen, China; [2]Key Lab. of Carcinogenesis and Translational Res. (Ministry of Educ. of China), Peking Univ. Cancer Hosp. & Inst., Beijing, China; [3]Dept. of Neurobio., Northwestern Univ., Evanston, IL

Abstract: Wnts are a family of secreted lipid-modified signaling proteins that act as short- or long-range signaling molecules in the regulation of cellular processes like proliferation, differentiation, migration, cell polarity during the development of nervous systems, as well as cardiac differentiation and development. We have recently demonstrated that Wnt signaling plays critical roles in the development of chronic pain after nerve injury or bone cancer through the canonical β-catenin-dependent and noncanonical β-catenin-independent pathways as well as the transcription factor YAP/TAZ nuclear-gate control. We hypothesized that a prolonged morphine exposure may serve as a severe stress that elicits neuronal alterations and activates Wnt signaling. Preventing and treating opioid dependence and withdrawal is a major clinical challenge and the underlying mechanisms of opioid dependence and withdrawal remain elusive. Here, we report that activation of Wnt signaling in the primary sensory neurons and the spinal cord plays critical roles in the development of opioid dependence. Our experiments were performed in a well-characterized mouse model of repeated using of morphine. The results show that Wnt5b is produced and accumulated in the dorsal root ganglia following repeated morphine treatment and that, following naloxone-precipitated withdrawal, the accumulated Wnt5b can be quickly transmitted to the spinal cord. In the spinal dorsal horn, Wnt5b, through the atypical Wnt-Ryk receptor and alternative Wnt-YAP/TAZ signaling pathways, contributes to the naloxone-precipitated opioid withdrawal-induced behavioral symptoms and hyperalgesia as well as the neurochemical alterations. Spinal blockade of Wnt-Ryk receptor and Wnt-YAP/TAZ signaling axes can greatly suppress the behavioral and neurochemical alterations after naloxone-precipitated withdrawal. These findings indicate a critical mechanism underlying the opioid dependence and naloxone-precipitated opioid withdrawal and suggest that targeting Wnt5b synthesis in the primary sensory neurons and Wnt signaling pathways in Wnt-Ryk and Wnt-YAP/TAZ signaling axes may be an effective approach for prevention and treatment of opioid dependence and the withdrawal syndromes.

Disclosures: **M. Wu:** None. **Z. Li:** None. **L. Liang:** None. **P. Ma:** None. **D. Liu:** None. **F. Rao:** None. **X. Song:** None.

Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.18/K20

Topic: D.03. Somatosensation – Pain

Support: Cinvestav-IPN

Title: The combination of morphine and haloperidol reduces allodynia and side effects of morphine in rats with neuropathic pain

Authors: *L. C. MENA-VALDÉS[1], Y. BLANCO-HERNÁNDEZ[1], A. MÉNDEZ-BERNAL[2], I. MARTÍNEZ-RACINE[2], J. V. ESPINOSA-JUÁREZ[1], F. J. LÓPEZ-MUÑOZ[1];
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Abstract: Haloperidol has been described as anti-nociceptive drug mediated by sigma 1 receptors antagonism. The morphine is an opioid drug currently used in the neuropathic pain (NP) treatment. **Objectives.** To determine the anti-allodynic effects of the combined therapy of haloperidol/morphine in rats with NP induced by chronic constriction injury (CCI),to evaluate the tissular damage produced in the CCI model and to detect the side effects of this combination. **Methods.** The anti-allodynic effects of haloperidol (0.01778mg/kg, s.c.) and morphine (0.0316mg/kg, s.c.) combination were determined after multiple-doses, using the cold allodynia test. The evaluations of cold allodynia were done until 10 days post-surgery every day, during one week andtissue samples (sciatic nerve and spinal ganglia) were taken on days 3, 6 and 9 to assess the severity of the damage before treatments. The rotarod test was used to evaluate motor coordination and for evaluate the effect of constipation was carried out a gastrointestinal transit test by using charcoal. **Results.** The time courses analysis indicated that morphine (0.0316mg/kg, s.c.) reached its maximum effect (≈60%) at day 4, which decreases abruptly from day 5 until values similar to the control. These results indicates that tolerance to the opioid was developed. However, the combination achieves a maximum anti-allodynic effect at day 2 (≈90%), which was maintained the next 5 days of evaluation, being significantly ($p < 0.0100$) greater than the maximum effect achieved by morphine. Histological analyse showed that CCI in control animals was characterized by several neutrophils, lymphocytes, macrophages and multinucleated cells in sections of the peripheral nerve and the spinal ganglia sections L5, L6 exhibit neuronal soma variably degenerate. On the other hand, the combination analysed did not show adverse effects of constipation or motor incoordination. **Conclusion.** The combination evaluated showed significant antiallodynic effects and did not present adverse effects, which suggest the use of this combination in NP treatment.

Disclosures: **L.C. Mena-Valdés:** None. **Y. Blanco-Hernández:** None. **A. Méndez-Bernal:** None. **I. Martínez-Racine:** None. **J.V. Espinosa-Juárez:** None. **F.J. López-Muñoz:** None.

Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

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Topic: D.03. Somatosensation – Pain

Support: NIH Grant R01DA034749
NIH Grant 1R01DA047089-01
NIH Grant 1R01DA047157-01

Title: Spinal PGC-1a suppressed morphine tolerance through reducing oxidative stress

Authors: Y. KASHIWAGI[1,2], H. YI[1], K. TAKAHASHI[1,2], K. HAYASHI[1], S. LIU[1], T. IIDA[1,2], J. GU[1], T. KUNISAWA[2], ***S. HAO**[1];
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Abstract: Long-term use of opioid analgesics is limited by the development of unwanted side effects, such as tolerance, and dependence, which contributes to the current epidemic of opioid abuse and overdose-related deaths in the U.S. The exact molecular mechanisms of morphine antinociceptive tolerance (MT) is still not clear yet. Previous evidence showed that MT induces neuroinflammation and oxidative stress in the spinal neurons. Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is crucial to mitochondrial function. It is not clear about the role of PGC-1a in morphine tolerance (MT) state. We hypothesize that spinal PGC-1α suppressed morphine tolerance through reducing mitochondrial superoxide. MT was induced by repeatedly intrathecal morphine twice daily for 7 days. Mechanical threshold and thermal latency were measured using von Frey test and hot plate test. MT lowered expression of spinal PGC-1α using western blots, and increased mitochondrial superoxide using mitochondrial superoxide image. Immunohistochemistry shows that the expression of PGC-1α and mitochondrial superoxide localized in the neurons of the spinal cord dorsal horn in MT rats. MT also induced the loss of the anti-oxidative SIRT3-MnSOD system. Intrathecally recombinant PGC-1α or Mito-Tempol (a mitochondrial scavenger) was given before morning morphine once daily for 7 days. Intrathecal recombinant PGC-1α, SIRT3, or Mito-Tempol reduced MT development in the von Frey test and hotplate test, left-shifted the curve of accumulated morphine. Intrathecal recombinant PGC-1α reduced the number of mitochondrial superoxide positive cells. The present findings suggest that PGC-1α, SIRT3-MnSOD, mitochondrial superoxide are involved in spinal MT, and that PGC-1α mediated mitochondrial superoxide in MT.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.20/K22

Topic: D.03. Somatosensation – Pain

Support: NIDA DA042565-01
NSF GRFP

Title: Diverse cell types within the vlPAG exhibit opioid-induced GIRK currents

Authors: *K. B. MCPHERSON, K. L. SUCHLAND, S. L. INGRAM;
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Abstract: The periaqueductal grey (PAG) is an important integration site within the descending pain modulatory pathway that receives diverse inputs—the ventrolateral region in particular (vlPAG) is a key target for opioid induced analgesia. The disinhibition theory for descending pain modulation proposes that opioids selectively inhibit GABAergic interneurons within the vlPAG, disinhibiting glutamatergic output neurons that project to the rostral ventromedial medulla (RVM). However, the vlPAG is a highly heterogeneous region with diverse cell types. Using whole-cell patch-clamp recordings of membrane firing properties in naïve rats we defined 5 distinct cell-types within the vlPAG: onset-firing, tonic firing, phasic firing, random-firing, and pacemaker neurons. These cell types are observed throughout the rostral-caudal axis without any obvious topographical distribution or morphological distinction. The firing properties were found to be intrinsic by removing GABAergic and glutamatergic tone. We examined opioid activation of G-protein coupled inwardly-rectifying potassium channel (GIRK) currents using the selective mu-opioid receptor agonist DAMGO. Unexpectedly, opioid-induced GIRK currents were observed in all of the cell types, and opioid-insensitive cells were also observed in all groups suggesting further heterogeneity within the vlPAG. Additional studies will use retrograde fluorescent CTb labeling from the RVM to examine the intrinsic properties of vlPAG neurons that project to this key downstream target for pain modulation and whether these cells are directly affected by acute or persistent inflammation. Collectively, these findings indicate that aspects of the disinhibition theory are over-simplified and that careful delineation of the circuits between the vlPAG and RVM will enhance our understanding of the descending control of pain.

Disclosures: **K.B. McPherson:** None. **K.L. Suchland:** None. **S.L. Ingram:** None.

Poster

484. Somatosensation: Pain and Opioids

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Topic: D.03. Somatosensation – Pain

Support: NIDA Grant DA044481
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New York Stem Cell Foundation
T32GM089626 Fellowship

Title: A suite of knockin mouse lines to resolve the functional organization of opioid receptors in neural circuits

Authors: *W. M. MCCALLUM[1], D. WANG[2], A. SHUSTER[3], D. J. BERG[4], S. LOW[6], G. SCHERRER[5];
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Abstract: Investigating opioid receptor-expressing neurons has been hampered by the lack of tools to gain specific genetic access to these cells. To address this issue, we generated knockin mouse lines in which we targeted the *Oprd1* and *Oprm1* genes that encode the delta and mu opioid receptors (DORs and MORs, respectively) to express the DNA recombinases Cre, CreERT2, Flp or Dre. These mouse lines can be used independently or combinatorically to selectively manipulate neurons expressing DOR, MOR, or both receptors. Here, we describe the characterization of *Oprd1*^{Cre} mice. To identify CNS neurons with Cre activity in adult mice, we first used either intra-cranial and -spinal injections of rAAV5-CAG-FLEX-GFP or intravenous (iv) injections of AAVPHP.eB-CAG-DIO-GFP. In the brain, we found that the Cre activity distribution pattern in *Oprd1*^{Cre} mice is remarkably consistent with the known expression pattern of DOR in wildtype mice, for example with GFP+ layer II/III and V cortical neurons, basolateral amygdala neurons, and striatal neurons. In the spinal cord, we observed GFP+ neurons throughout the grey matter, including in the ventral horn, and with a particularly high density at the ventral border of lamina II inner, confirming our recent findings (Wang et al., 2018) with an independent tool. To examine *Oprd1* expression in DRG neurons, we made iv injections of AAVPHP.S-CAG-DIO-GFP to *Oprd1*^{Cre} mice. We also crossed *Oprd1*^{Cre} mice with Ai14 (*Rosa26* $^{LSL\text{-}tdTomato}$) and *Oprd1*^{GFP} mice to compare the *Oprd1* expression fate map (*Oprd1* lineage) and *Oprd1* expression pattern in the adult mouse. These studies revealed the remarkably dynamic expression of DOR through embryonic development, during which considerably more

DRG neuronal types express *Oprd1*, including peptidergic C nociceptors that express *Oprm1*, before DOR expression in these cells is extinguished postnatally. Thus, in the adult, Cre activity is largely restricted to myelinated mechanosensory neurons, as evidenced by the presence of tdTomato+ and GFP+ large diameter DRG neurons with axons that project both to spinal laminae III-IV and to medullary cuneate and gracile nuclei through the dorsal column pathway. Collectively, our data establish the utility of *Oprd1*^{Cre} mice to investigate and manipulate DOR-expressing neurons, and begin to define the temporal and spatial characteristics of *Oprd1* and *Oprm1* (co)-expression for elucidating the functional organization of the opioid system.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.22/K24

Topic: D.03. Somatosensation – Pain

Support: Funding provided by Stanford Medical Scholars Fellowship program
NIH R00DA031777
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Title: Architecture of opioid-mediated neuromodulation of sensory, motor, and respiratory brainstem circuits

Authors: N. F. HUG, *N. MERCER LINDSAY, W. M. MCCALLUM, G. SCHERRER; Stanford Univ., Stanford, CA

Abstract: Opioids profoundly alter sensory responses, motor behaviors, and respiratory activity. However, the distribution pattern of opioid receptors in brainstem circuits has not been clearly elucidated. Here we examined the expression patterns of mu and delta opioid receptors (MOR and DOR respectively) in sensory and motor circuits in the brainstem using antibodies and MOR-mCherry/DOR-eGFP reporter mice.
We found that that DOR and MOR are expressed in oral sensory and motor nuclei. We observed notable labeling in the secondary sensory neurons in the dorsal part of the principal sensory nucleus as well as in the motor neurons for the esophagus, lips, and tongue. These findings in oral circuits prompted us to look in detail at labeling of MOR and DOR in other brainstem structures involved in breathing, with an emphasis on the pre-Bötzinger Complex (PBC), the central pattern generator for breathing.

Opioid-induced respiratory depression (OIRD) is the leading cause of opioid-related overdose deaths in the United States. While there is significant evidence for the direct impact of opioids on respiration, there is little agreement on where the site of action is within the brain. Therefore, we next aimed to identify MOR+ and DOR+ neurons in the PBC area.
Specifically, we examined the PBC MOR+ neurons for overlap with other classic markers of PBC rhythmic respiratory neurons: somatostatin (SST) and neurokinin-1 receptor (NK1R). Using immunohistochemistry (IHC), we found that MOR+ neurons are present in the PBC in a partially overlapping but distinct population from the canonical rhythmogenic neurons. Further, we found a distinct DOR+ neuron population in the PBC that also partially overlaps with MOR+ neurons. To validate these findings, we also performed in situ hybridization experiments in wildtype mouse tissue with probes against *Oprm1* (gene encoding MOR) and *Sst* transcripts and found the same pattern of expression as in IHC experiments.
Taken together, these results suggest that opioids may act both on cranial motor nuclei and PBC circuits to impair breathing. The studies begin to elucidate opioid receptor organization in brainstem to resolve the circuit and molecular mechanisms that underlie OIRD.

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Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.23/K25

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DE17794
NIH Grant DE22743

Title: PD1 modulates nociceptive synaptic transmission and mu opioid receptor signaling in the spinal cord dorsal horn

Authors: *C. JIANG[1], Z. WANG[2], M. MATSUDA[2], Q. HE[2], R.-R. JI[3];
[1]Dept. of Anesthesiol., Duke Univ. Med. Ctr., DURHAM, NC; [3]Pain Res. Division, Anesthesiol., [2]Duke Univ. Med. Ctr., Durham, NC

Abstract: Programmed cell death ligand-1 (PD-L1) is typically produced by cancer cells and has been shown to suppress immunity through PD-1 receptor expressed on T cells. However, neuronal signaling of PD-1 is largely unknown. Recently we demonstrated that PD-1 is also expressed by primary sensory neurons and mediates PD-L1-evoked synaptic transmission (Chen et al., 2017). Here we tested if PD-1 is involved in neurotransimminon induced by opioid. One key mechanism for opioid analgesia is to decrease neurotransmitter release and nociceptive

synaptic transmission in the spinal cord dorsal horn (SDH), which is mainly mediated by an activation of mu opioid receptor (MOR). Double staining revealed co-localization of PD-1 and MOR immunoreactivity in SDH axons and axonal terminals. We prepared mouse spinal cord slices to record spontaneous excitatory postsynaptic currents (sEPSCs) in out lamina II neurons. Bath perfusion of morphine (10 μM) in spinal cord slices of WT mice led to a significant reduction of sEPSC frequency. However, in P*d1*-deficient spinal slice, this inhibition was suppressed. Next, we compared morphine-evoked outward currents in SDH neurons in WT and KO mice. We found that the average amplitude of outward currents was changed from 15.8 ± 1.5 pA in WT mice to 7.8 ± 1.8 pA in KO mice ($P < 0.05$). To confirm that MOR signaling needs PD-1, we also tested morphine effect on synaptic transmission in spinal slices treated with Nivolumab, a clinically used anti-PD-1 monoclonal antibody or control IgG. We found that Nivolumab treatment also reduced morphine's inhibition on EPSC. Finally, we found that PD-L1 (0.075 nM), a major ligand of PD-1, and morphine (0.01 nM) produced synergistic actions in synaptic
transmission inhibition. Taken together, our data demonstrate that PD-1 is an essential signal imponent of MOR signaling in nociceptive synaptic transmission in the spinal cord dorsal horn.
References
Chen G, Kim YH, Li H, Luo H, Liu DL, Zhang ZJ, Lay M, Chang W, Zhang YQ, Ji RR (2017). Nat Neurosci. 2017, Jul;20(7):917-926

Disclosures: **C. Jiang:** None. **Z. Wang:** None. **M. Matsuda:** None. **Q. He:** None. **R. Ji:** None.

Poster

484. Somatosensation: Pain and Opioids

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 484.24/K26

Topic: D.03. Somatosensation – Pain

Support: NIH Grant DE17794
NIH Grant DE22743

Title: Neuronal PD-1 (programmed cell death protein-1) is required for morphine analgesia and mu opioid receptor signaling

Authors: *Z. WANG, C. JIANG, M. MATSUDA, K. WANG, J. ZHAO, R.-R. JI;
Duke Univ., Durham, NC

Abstract: Opioids such as morphine produce analgesia via mu opioid receptor (MOR). Despite extensive research in last several decades, opioid receptor signaling is not fully understood. Programmed cell death ligand-1 (PD-L1) is an immune checkpoint inhibitor and suppresses immunity through PD-1 receptor expressed on immune cells. However, PD-1 signaling in

neurons is largely unknown. We recently reported that primary sensory neurons of dorsal root ganglion (DRG) express PD-1 receptor, and activation of PD-1 by PD-L1 inhibits neuronal excitability and pain[1]. This study was undertaken to investigate the interactions between PD-1 and MOR, two inhibitory and analgesic receptors in the peripheral and central nervous system. We used *Pd1* knockout mice and anti-PD-1 monoclonal antibody, nivolumab to investigate the PD-1 effects on morphine analgesia in tail-flick and hot plate tests, CFA induced inflammatory pain, SNL induced neuropathic pain and bone cancer pain models. Our results indicated that morphine induced antinociception in tail-flick and hot plate tests, and anti-allodynic effects in CFA induced inflammatory pain, SNL induced neuropathic pain and bone cancer pain models was impaired in *Pd1* knockout mice. Moreover, morphine analgesia was also abrogated in adult wild-type mice after treatment with Nivolumab, a clinically used anti-PD-1 monoclonal antibody. Notably, PD-1 and MOR are highly colocalized in DRG neurons and have functional interactions. The suppressing effects of morphine in calcium currents in DRG neurons was also impaired in *Pd1* knockout mice. Finally, PD-L1 and morphine produce synergistic analgesia. Our findings suggested that anti-PD-1 immune therapy may interfere opioid analgesia in cancer patients via disrupting the PD-1-MOR interaction in the peripheral nerve and DRG tissue. On the other hand, PD-L1 might be used to treat clinical pain and enhance opioid analgesia in cancer and non-cancer patients.

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References

1. Chen G, Kim YH, Li H, Luo H, Liu DL, Zhang ZJ, Lay M, Chang W, Zhang YQ, Ji RR (2017). Nat Neurosci. 2017, Jul;20(7):917-926

Disclosures: Z. Wang: None. **C. Jiang:** None. **M. Matsuda:** None. **K. Wang:** None. **J. Zhao:** None. **R. Ji:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 485.01/K27

Topic: D.04. Somatosensation – Touch

Title: Peripheral nerves are invoved in human skin elasticity

Authors: *M. TSUTSUMI, K. TAKAGAKI, S. NOMIYAMA, K. KAJIYA;
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Abstract: Cutaneous innervation is essential for the perception and maintenance of skin homeostasis. Until now, intra epidermal nerve fibers have been studied as a potential cause for symptoms like itchiness, pain, and abnormal sensations. Previous reports describe peripheral nerve fibers as having a crucial role on epidermal functions. Detailed morphologies of nerve

fibers in the dermis and their role remain unclear. The dermis provides tissue integrity and elasticity. Collagen is the major structural protein of the extracellular matrix and is synthesized by dermal fibroblasts. We have demonstrated the 3D structure of peripheral nerves in the dermis and investigated how they affect dermal elasticity.
Light Sheet Fluorescence Microscopy (LSFM) is superior to conventional microscopy for precise imaging of large specimens with exceptional light efficiency and speed. First, we used LSFM to construct 3D images of peripheral nerve fibers in the facial skin of healthy subjects. Skin tissues were clarified and immunolabeled for PGP9.5. This method allowed us to observe their 3D structure in a dermal area almost 2 mm below the epidermis. Deeper in the dermis, nerves bundle vertically toward the epidermis and formulate dense networks by branching in the upper region of the dermis. To investigate the change of density in nerve fibers during aging, we quantified the volume of nerve fibers (PGP9.5 and Neurofilament H) using 50 μm cross sections. Nerve fibers were denser in younger groups (mean age 34.8±8.0. 27, 33, 33, 46 years) compared to older groups (mean age 75.5±15.1. 57, 70, 84, 91 years). Next, to explore the effects of neuro-mediators released from neurons on fibroblasts, Human iPSC-Derived Sensory Neuron Progenitors were cultured. Cultured fibroblasts were treated with a neural conditioned medium and collagen I mRNA was measured. As a result, the medium upregulated collagen mRNA expression. In addition, we observed continuous procollagen synthesis in skin explants using immunohistochemistry. Since procollagen is the precursor molecule of collagen, it suggests collagen synthesis is newly occurring, not there for the maintenance of existing collagen I. These results suggest that the degradation of nerve fibers from aging would lead to be a reduced skin elasticity. In conclusion, the peripheral nervous system has a crucial role in skin homeostasis, not only for epidermal functions but also in dermal elasticity.

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Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 485.02/K28

Topic: D.04. Somatosensation – Touch

Support: DFG SCHW 577/14-1
DFG BR 1689/9-1

Title: Human fingertip sensitivity to local coding variables of vibrotactile stimuli

Authors: A. BHATTACHARJEE, C. BRAUN, *C. SCHWARZ;
Univ. of Tuebingen, Tuebingen, Germany

Abstract: Vibrotactile skin deflections are the basis for texture identification. Classically, it has been assumed that global temporal variables ‘intensity’ (time-averaged kinematics), or ‘frequency’ (best frequency inferred from spectral analysis) dominate vibrotactile discrimination. Here, driven by the idea that short lived frictional skin deflection, so called ‘stick-slip’ movements, may be instrumental (Schwarz 2016, TINS 39:449), we test the alternative idea that local temporal aspects of the vibrotactile signal (instantaneous kinematics) support vibrotactile discrimination.
We used pulsatile stimuli (pulse frequency, pf), in which a pulse consists of a single-period cosine. By choosing the pulse’s waveform frequency (wf) and amplitude (a), we varied local kinematics while being able to disentangle the global variables pf and intensity. In a Yes/No detection of change psychophysical paradigm the participants’ task was to determine whether a 1s series of pulses changed its character in the middle. In a first approach we designed pairs of discriminanda (first stimulus always a=40micron, pf=90Hz and wf=170 Hz) that differed solely in pf and thus not containing any local cue. Five out of 7 participants detected these changes at a threshold level of $\Delta pf \sim 15 \pm 5\%$ (mean±SD, i.e. at pf=103.5 Hz) showing that humans are able to use global variables in absence of local ones. Next, keeping pf and a constant, wf (and local variables) could be changed without affecting the mean speed. Six out of 7 participants mastered the task at an average threshold of $\Delta wf \sim 25 \pm 5\%$ (i.e. at wf= 212Hz) suggesting that - assuming intensity is measured as mean speed - humans can base their perception purely on local variables. Finally, aiming at relaxing the assumption that intensity is only measured as mean speed, we systematically examined the 8-dimensional stimulus space spanned by local velocity and acceleration; and global parameters mean(absolute(velocity^x)) and mean(absolute(acceleration^x)) (with x=[1,2,3]) to identify pairs of discriminanda that would disentangle these versions of intensity and local velocity. A favorable situation was found at wf=198Hz, where two test stimuli were available, distinguishing the effect of local velocity. All participants’ performance was better at detecting stimuli that included local velocity cues vs those excluding it (percent correct: 72% vs. 40%; paired t-test; p=0.002). In summary, our data provide first evidence that humans are sensitive to local tactile coding features, opening the possibility that they may use frictional movements as a basis of texture identification.

Disclosures: A. Bhattacharjee: None. **C. Braun:** None. **C. Schwarz:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 485.03/K29

Topic: D.04. Somatosensation – Touch

Support: FP067238-02-PR

Title: Characterizing the tactile sensitivity of the breasts

Authors: *K. R. MCLELLAN[1], K. H. LONG[2], A. K. SURESH[1], S. LINDAU[1], S. J. BENSMAIA[3];
[2]Interdisciplinary Scientist Training Program, sp. Computat. Neurosci., [3]Dept. of Organismal Biol. and Anat., [1]Univ. of Chicago, Chicago, IL

Abstract: Simple (or total) mastectomy, the most common mastectomy procedure for women with breast cancer, involves amputating all of the breast tissue, including the cutaneous branches of intercostal nerves III-VI. The resulting loss of sensation in the breast leads to a feeling of disembodiment and can cause sexual dysfunction. To develop strategies for preserving or restoring breast function, we characterize the neural basis of breast sensation in healthy women. First, we assess which classes of tactile nerve fibers innervate the breast. Second, we identify the role of individual intercostal nerves in carrying sensory signals from the breast. To these ends, we designed and constructed an experimental apparatus to passively deliver diverse, well-controlled tactile stimuli to the breast and nipple-areolar complex (NAC). We then present a variety of tactile stimuli - including vibrations and textures - and have subjects perform perceptual judgments adapted from well-established psychophysical paradigms used to investigate the tactile sensitivity of the hand. After establishing the baseline sensitivity of the breast, we pharmacologically block individual intercostal nerve fibers to assess each nerve's contribution to sensation.

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Poster

485. Touch: Transduction and Stimulus Encoding

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Program #/Poster #: 485.04/K30

Topic: D.04. Somatosensation – Touch

Support: NIH grant DE018661
NIH grant DE023090

Title: Differential effects of potassium channel blockers on mechanical responses of three types of mechanoreceptors in whisker hair follicles of mice

Authors: M. SONEKATSU[1,2], A. YAMADA[1], J. LING[1], *W. TANIGUCHI[2], J. G. GU[1];
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Abstract: Mechanoreceptors are essential in tasks such as environmental exploration, social interaction and tactile discrimination. Using our newly developed pressure-clamped single-fiber recording technique, we have recently identified in whisker hair follicles of mice three functional types of mechanoreceptors, the rapidly adapting (RA), slow adapting type 1 (SA1) and slowly adapting type 2 (SA2) mechanoreceptors. In the present study we explored the role of K^+ channels in tuning impulse firing of these mechanoreceptors by testing effects of different K^+ channel blockers on mechanically evoked whisker afferent impulses. We tested tetraethylammonium (TEA) and found that neither RA nor SA1 impulses were affected by bath application of 10 mM TEA, but SA2 impulses were significantly increased by TEA at the concentrations of 5 mM and 10 mM. However, SA2 impulses were suppressed by TEA at the lower concentrations of 200 µM and 1 mM. We tested 4-aminopyridine (4-AP) and found that RA impulses were not affected by bath application of 1 mM 4-AP, but both SA1 impulses and SA2 impulses were suppressed by 1 mM 4-AP. At a lower concentration of 100 µM 4-AP, SA2 impulses but not SA1 impulses were suppressed. We tested Ba^{2+} and found that both RA and SA1 impulses were increased but SA2 impulses suppressed by bath application of 5 mM Ba^{2+}. When these K^+ channel blockers were focally applied to whisker afferent nerves but not applied to whisker hair follicles, they did not have any effects on the impulses of these mechanoreceptors. These findings suggest that different types of K^+ channels may be differentially expressed at the afferent terminals of these mechanoreceptors in whisker hair follicles to tune their functions.

Disclosures: M. Sonekatsu: None. **A. Yamada:** None. **J. Ling:** None. **W. Taniguchi:** None. **J.G. Gu:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 485.05/K31

Topic: D.04. Somatosensation – Touch

Support: NIH grant DE018661
NIH grant DE023090

Title: Impairment of slowly adapting type 1 mechanoreceptors in mice following vincristine treatment

Authors: *M. S. SONEKATSU, J. G. GU;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Loss of the sense of touch or numbness in fingertips and toes is one of the most common sensory dysfunctions in patients receiving chemotherapy with anti-cancer drugs such as

vincristine. Whisker hair follicles functionally resemble human fingertips and contain several types of mechanoreceptors including lanceolate endings, Merkel discs and Ruffini-like endings. Electrophysiologically, Lanceolate endings, Merkel discs and Ruffini-like endings in whisker hair follicles mediate rapidly adapting (RA), slowly adapting type 1 (SA1), and slowly adapting type 2 (SA2) responses, respectively. In the present study, we investigated effects of vincristine treatment on each type of mechanoreceptors in whisker hair follicles of mice. Nerve impulses of each type of mechanoreceptors were elicited by mechanical stimulation to whisker hair follicles and recorded using our newly developed pressure-clamped single-fiber recording technique. *In vitro* short-term treatment of whisker hair follicles with 2 μM vincristine for 2 hours increased mechanically evoked impulses of RA and decreased SA1 significantly, but did not affect the impulses of SA2. *In vivo* treatment of animals with vincristine at a daily dose of 0.3 mg/kg for 10 days significantly decreased mechanically evoked impulses of SA1, but had no significant effects on impulses of RA and SA2. Collectively, our results suggest that Merkel discs, the mechanoreceptors mediating SA1 responses in whisker hair follicles, are main targets by vincristine to cause the impairment of tactile sensitivity.

Disclosures: M.S. Sonekatsu: None. **J.G. Gu:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

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Program #/Poster #: 485.06/K32

Topic: D.04. Somatosensation – Touch

Support: CIHR Operating Grant (AC)
NSERC Discovery Grant (AC)

Title: Integrin alpha1 beta1 increases mechanosensation and decreases cold perception in the mouse hind paw

Authors: J. MICHAUD[1], S. LEE[1], V. WAI[1], A. POZZI[2], L. BENT[1], *A. L. CLARK[1];
[1]Univ. of Guelph, Guelph, ON, Canada; [2]Vanderbilt Univ., Vanderbilt, TN

Abstract: Objective: To measure the effect of integrin α1β1 on mechanical and temperature sensation in the mouse hind paw.
Rationale: Integrin α1β1 is a collagen receptor expressed by keratinocytes in the basal layer of the epidermis. Merkel cells and Meissner's corpuscles (MCs) are low-threshold mechanoreceptors found in close proximity to integrin α1β1 in the basal epidermis. Furthermore, MCs are tethered to the basal epidermis by collagen fibres. Transient receptor potential vanilloid 4 (TRPV4) is highly expressed by epidermal keratinocytes, Merkel cells and MCs. TRPV4 is activated by warm temperatures (>27°C) and osmotic stress, and TRPV4 deficient mice show

deficits in heat detection. Interestingly, integrin α1-null cells are insensitive to osmotic stress, suggesting that integrin α1β1 is necessary for the function of TRPV4. Therefore we hypothesize that integrin α1-null mice have reduced mechanical and heat sensation in the hind paw.
Methods: All animal procedures were approved by the University of Guelph ACC. 20 adult wildtype (WT) and integrin α1-null (KO) mice (10 of each sex) were exposed to 3 assays for mechanosensation (ramping Von Frey, static Von Frey (0.8-7.5g hairs) and cotton swab) and 2 assays for thermosensation (hot plate (50°C) and ice pack (-20°C)). For ramping Von Frey, an electronic anesthesiometer was applied and the force output recorded when a response was elicited. For all assays, flicking, licking or withdrawal of the hind paw constituted a response. ANOVA with genotype and sex as factors were conducted for all data except the static Von Frey where a repeated measures ANOVA was applied.
Results: KO and female mice had a lower threshold of response to ramping Von Frey compared to WT ($p=0.03$) and male ($p=0.04$) mice respectively. There were fewer responses ($p=0.001$) to the 7.5g hair by KO mice compared to WT, and no effects on the cotton swab assay. There was a significant ($p=0.004$) sex and genotype interaction effect for the cold plate test, with male KO mice showing 5s less tolerance compared to male WT and female KO mice. Heat tolerance was less in females compared to males ($p=0.03$), with no genotype effect.
Conclusions: Integrin α1β1 increases the force threshold for mechanosensation by 1g, but does not influence light touch. This suggests that integrin α1β1 influences the function of Merkel cells but not MCs. Surprisingly, integrin α1β1 increases cold tolerance but only in male mice, and does not influence heat sensation. This suggests that compensatory mechanisms are at play to restore the lost heat responses due to TRPV4 dysfunction in KO mice.
Significance: Integrin α1β1 plays an important role in hind paw mechanical and temperature sensation.

Disclosures: J. Michaud: None. **S. Lee:** None. **V. Wai:** None. **A. Pozzi:** None. **L. Bent:** None. **A.L. Clark:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: CIHR Operating Grant (AC)
NSERC Discovery Grant (AC)

Title: The density of Meissner's corpuscles varies with anatomical location across the sole of the hind paw, but is not affected by integrin alpha1beta1

Authors: *V. WAI, L. ROBERTS, L. BENT, A. L. CLARK;
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Abstract: Introduction: Balance and motor control are influenced by mechanoreceptors in the glabrous skin of the foot. Studies utilizing microneurography show a concentration of afferent responses in the anterolateral human foot sole, however mechanoreceptor density at the afferent terminals is unknown. Meissner's corpuscles (MCs) are mechanoreceptors responsible for sensing light touch, grip and low frequency vibrations, whose function is conserved across mammalian species. MCs are located in the dermal papillae where they are tethered to the stratum basale by collagen fibres. The collagen receptor, integrin α1β1, is expressed by keratinocytes in the basal layer of the dermis. The proximity of integrin α1β1 to MCs may suggest interplay between them, affecting mechanosensation. We hypothesize MC density will be greatest in the anterolateral hind paw footpads and will be increased in integrin α1-null (KO) compared to wild type (WT) mice.
Methods: Animal procedures were approved by the University of Guelph ACC. 16 right hind paws were harvested from WT and KO mice (8 of each sex). Hind paws were fixed (4% PFA), processed, embedded (paraffin) and serially sectioned (8μm) in the sagittal plane. Every third slide was stained using hematoxylin and eosin, and imaged using light microscopy. MCs were counted every 90μm and density was calculated as a function of foot pad or phalanx surface area. Repeated measures ANOVA with genotype and sex as factors were conducted for MC density in footpads and distal phalanges, and footpad surface area.
Results: The surface area of footpad 5 was three times greater than the other footpads ($p<0.001$). MCs were found exclusively in the dermal papillae of the footpads and the tips of the distal phalanges. On average, MC density was at least five times greater in the footpads ($12.5mm^{-2}$) than the phalanges ($2.2mm^{-2}$). MC density was on average at least three times greater in footpads 1, 3, 4 ($19.4mm^{-2}$) compared to footpads 2, 5, 6 ($5.7mm^{-2}$), and three times greater in phalanges 2 and 5 ($3.2mm^{-2}$) compared to phalanges 3 and 4 ($1.0mm^{-2}$). Genotype and sex had no effect on MC density or footpad size.
Conclusion: MC localization to the footpads and distal phalanges suggests that these are critical contact regions providing mechanosensation feedback in mice. Larger MC density in footpads 1, 3, and 4 may suggest the importance of these pads in anteroposterior balance control while larger MC density in phalanges 2 and 5 may suggest their role in mediolateral gripping and balance control.
Significance: Differences in MC density across the footpads and distal phalanges suggests their anatomical location is critical in anteroposterior and mediolateral balance respectively.

Disclosures: V. Wai: None. **L. Roberts:** None. **L. Bent:** None. **A.L. Clark:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Program #/Poster #: 485.08/K34

Topic: D.04. Somatosensation – Touch

Support: NS 101325

Title: Dependence of texture-elicited skin vibrations on scanning speed

Authors: *C. M. GREENSPON, K. R. MCLELLAN, J. D. LIEBER, S. J. BENSMAIA; Organismal Biol. & Anat., Univ. of Chicago, Chicago, IL

Abstract: We are exquisitely sensitive to surface microstructure and to the material properties of objects. To sense the finest elements of a texture - measured in the tens of nanometers - requires movement between the skin and a surface, which elicits vibrations in the skin that are dependent on both the texture and the way it is explored. These vibrations can be measured using a laser Doppler vibrometer that measures the movement of the skin along the axis perpendicular to its surface. With this technique, texture-elicited vibrations have been shown to depend on the speed at which the skin moves over the surface. Indeed, the vibrations dilate or contract with increases or decreases in scanning speed, respectively. While the effect of scanning speed on the frequency composition of skin vibrations has been characterized, its effect on their intensity has not. To do so requires that textures be scanned at different speeds within the same experimental block, so that the effective gain of the measurement remain consistent across speeds. To fill this gap, we presented textures to the fingertips of human participants scanned over a range of speeds (10 - 160 mm/s) and measured the skin vibrations using a laser-Doppler vibrometer. We replicated the result that, as speed increases, the frequency composition of the vibrations shifts systematically towards higher frequencies, leading to a constant frequency when expressed in spatial units. Furthermore, vibratory intensity - as gauged by root mean squared displacement - increased with speed. We found that the warping of the frequency composition of the vibrations - its shift toward the left or the right with decreases or increases in scanning speed - could account for the bulk of the effect of scanning speed on intensity. We could further improve the fit by taking into account the resonance of the skin, which selectively modulates frequencies. Our model allows us to predict the vibratory power at any speed for any texture given the power spectrum of that texture at any one speed.

Disclosures: C.M. Greenspon: None. **K.R. McLellan:** None. **J.D. Lieber:** None. **S.J. Bensmaia:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: ESA
Prodex (BELSPO, Belgian Federal Government)
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Title: Imaging the fingerpad deformations during vertical oscillations of a hand-held object

Authors: *B. P. DELHAYE[1], F. SCHILTZ[1], J.-L. THONNARD[1], P. LEFEVRE[2];
[1]Univ. Catholique de Louvain, Brussels, Belgium; [2]Univ. Catholique de Louvain, Louvain-la-Neuve, Belgium

Abstract: Dexterous object manipulation critically relies on the feedback provided by the tactile afferents innervating the fingertips. Indeed, disruption of this feedback severely impairs our ability to properly coordinate the fingertip forces exerted on the object. The interactions between the fingertips and the object continuously generate complex spatiotemporal skin deformations that are in turn faithfully encoded by the afferents. To better understand the exact nature of those deformations and therefore the information that could potentially be captured by the skin afferents during active movements, we imaged the contact area between the index fingertip and a transparent object while subjects (n=6) performed vertical oscillations using a precision grip. A total of 300 oscillations were recorded for each subject, split into 15 blocks of 30 seconds. The oscillations peak-to-peak amplitude was 20 cm, and a metronome guided the pace at 1.5 seconds per cycle. From the images, we could then track fingerprints and evaluate skin strains in the contact area. We also monitored the interaction forces (i.e. the grip force and the load force) and torques, the fingerpad moisture before and after each block, and the coefficient of friction. Two major fingertip deformations took place at each oscillation cycle. First, due to fingertip compliance, the bulk of the fingerpad oscillated up and down, following the load force acting as a pulling force. This was characterized by rolling and associated motion of the center of pressure of the fingertip. Second, when the bulk movement approached its maximum, we observed the systematic occurrence of partial slips at the periphery of the contact area between the fingerpad and the object. Those partial slips occurred even though the object was still securely held between the fingers and resulted in patterns of skin strains that were highly stereotyped during an oscillation cycle. While the amount of partial slip was consistent across trials, it varied a lot across subjects due to various factors including the level of grip force, the coefficient of friction, the fingerpad moisture and the compliance of the skin. We argue that those partial slips and the

resulting strain patterns might provide essential information to adjust the grip force and avoid complete slip.

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Poster

485. Touch: Transduction and Stimulus Encoding

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Program #/Poster #: 485.10/K36

Topic: D.04. Somatosensation – Touch

Title: Consistency and discrepancy between reported direction and trajectory: Layered mechanisms of tactile motion perception

Authors: *S. KUROKI;
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Abstract: By sensing direction and trajectory of the motion across the skin, we are able to identify relative positional relationship of hand and touching object and local shape of the object. Motion direction perception has been well studied, and involvement of slow, high-level feature tracking mechanism has been suggested. Tactile motion aftereffect occurs at spatiotopic frame rather than somatotopic frame [Watanabe et al., EBR 2009; Kuroki et al., EBR 2012], and the threshold of direction detection is well beyond that of motion detection [Holcombe et al., Vision Res 2008; Kuroki et al., JNP 2016]. These studies indicates lack of low-level motion energy detector as observed for visual motion perception. On the other hand, motion cue is also essential for object manipulation, where not only accuracy but also rapidity is essentially required. Indeed, neurophysiological/computational studies suggested existence of tactile low-level motion/shape detectors [Delhaye et al., JNP 2019; Pei et al., PLoS Biol 2010; Pruszynski et al., NatNeurosci 2014]. Here we try to consider whether not only slow/high-level feature tracking but also fast/low-level mechanism of motion detection can contribute to motion feature perception. In the experiment, participants put their palm or medial side of the forearm on the braille display (32×48 array). One of four tilted motion stimuli (upward or downward, rightward or leftward) was presented. Participants were asked to report two questions: motion direction (up or down) and resulting shape of its trajectory (diagonal line between bottom left to top right or line between bottom right to top left). If our perceptual access is limited to position tracking mechanism, the shape of motion would be correctly answered only when the tracking is succeed, i.e., when the direction of motion is correctly detected. If, we can also access to the motion feature information extracted from low-level mechanism perceptually, then the proportion correct of these two questions does not necessarily correlated. We found that accuracies for direction and shape questions were not correlated when experiment was done with the palm, suggesting multiple mechanisms of tactile motion perception. Interestingly, the correlation was

found when the same task was conducted with arm, where is not frequently used for object manipulation. Note that the size of stimuli on the arm was quadruple of that on the palm, which was normalized based on the ability of two-point discrimination. These results support the idea that the brain uses multiple mechanisms depending on the situation and body site.

Disclosures: S. Kuroki: A. Employment/Salary (full or part-time):; NTT Communication Science Laboratories.

Poster

485. Touch: Transduction and Stimulus Encoding

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Program #/Poster #: 485.11/K37

Topic: D.04. Somatosensation – Touch

Support: Ontario Early Researcher Award
CIHR
BrainsCAN

Title: Fine orientation processing in the tactile periphery

Authors: *V. SUKUMAR[1], E. HAY[2], A. PRUSZYNSKI[3];
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Abstract: First-order tactile neurons signal information about touched objects. Previously, we showed that these neurons extract the geometric features such as edge orientation. Here, we probed the robustness and fidelity of this edge orientation processing for finely spaced edges presented over a wide range of stimulation speeds. We recorded from 56 human first-order tactile neurons - 32 fast-adapting Type-1 (FA-1) innervating Meissner corpuscles and 24 slow-adapting Type-1 (SA-1) innervating Merkel endings. The stimuli were edges embossed on a rotating drum, oriented 5 to 20 degrees relative to the fingertip, presented at 12 speeds from 2.5 to 270 mm/s speeds. Responses of both FA-1 and SA-1 neurons robustly discriminated the edges at slow and medium speeds using the temporal code. Intensity codes performed poorer. Contrary to previous notions about the relative specialization of SA-1 neurons for signaling fine spatial details, we found that FA-1 neurons carried more information about fine differences in edge orientation. Our results suggest that first-order tactile neurons signal fine edge orientations robustly across a broad range of speeds used during normal hand function, and that FA-1 neurons are particularly important for processing finer details of touched objects.

Disclosures: V. Sukumar: None. **E. Hay:** None. **A. Pruszynski:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: ERC Starting Grant 759998
Wellcome Trust 209998/Z/17/Z
Natural Sciences and Engineering Research Council (NSERC) (Grant ID 312007) of Canada

Title: Modeling tactile responses from the sole of the foot

Authors: *R. KAZU[1], N. KATIC[3], L. BENT[4], N. STRZALKOWSKI[5], S. RASPOPOVIC[6], H. P. SAAL[2];
[1]Dept. of Psychology and Sheffield Robotics, [2]Psychology, Univ. of Sheffield, Sheffield, United Kingdom; [3]Dept. of Signals and Systems, Univ. of Belgrade, Belgrade, Serbia; [4]Univ. Guelph, Guelph, ON, Canada; [5]Univ. of Calgary, Calgary, AB, Canada; [6]Dept. of Hlth. Sci. and Technol., ETH Zürich, Zuerich Eth-Zentrum, Switzerland

Abstract: Cutaneous feedback from the foot sole is crucial for gait and balance control. Four classes of specialized afferents innervate the skin of the soles of the feet and had their electrophysiological properties recently explored in detail with the aid of microneurography. Nevertheless, in order to fully understand their role in balance control and walking, and to devise more natural feedback for prosthetic limbs, afferent responses need to be studied at the population level.
Here, we present a computational model that simulates neural spiking responses from the combined population of mechanoreceptive afferents innervating the sole of the foot. Our work takes into account the unique mechanics of the skin tissue in the foot (including depth and hardness), and includes all relevant afferent classes (both slowly and rapidly adapting) that signal skin indentation, slip, vibration, and stretch. Single-unit recordings of afferent firing characteristics were used for validation and fitting. The work builds on previous research in our group on mechanotransduction in the hand.
We used the model to calculate receptive field sizes and thresholds (absolute and tuning) across afferent types and show that they match their empirical counterparts closely. We also quantified how skin mechanics affects the tactile responses across different regions of the foot.
In future work, we plan to use the model to improve somatosensory feedback in prosthetic devices through neural interfaces with lower limb nerves.

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Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: MEXT KAKENHI 16H06544
JSPS KAKENHI Early-Career Scientists 19K16283

Title: Different cell groups encode stimulus intensity and direction in insect mechanosensory system

Authors: *H. OGAWA[1], K. TANAKA[2], M. SOMEYA[3], H. SHIDARA[1];
[1]Dept. of Biol. Sciences, Fac. of Sci., [2]Biosystems Sci. Course, Grad. Sch. of Life Sci., Hokkaido Univ., Sapporo, Japan; [3]Lab. for Circuit Mechanisms of Sensory Perception, RIKEN CBS, Wako, Japan

Abstract: The sensory system extracts various characteristics of stimulus including intensity, frequency, and direction and encodes the sensory information by spike trains of cell population. Many neurophysiological studies have focused on neural codes of various sensory parameters. However, it remains unclear whether individual neurons encode only specific sensory parameter of the stimulus or are involved in representation of multiple stimulus characteristics. To address this issue, we used cricket cercal sensory system to detect airflow dynamics surrounding animal. The sensory information of airflow such as airflow speed and stimulus orientation is processed by local circuit within the terminal abdominal ganglion and conveyed to higher center via several identified projection neurons such as the giant interneurons (GIs). The previous study revealed that the direction of airflow is encoded by two pairs of GIs (Miller and Theunissen, 1991), but it is unknown what impacts the stimulus intensity has on the directional encoding. We measured the spike responses of individual GIs to airflow stimulus of various velocities from different angles using intracellular recording method and reported that the impacts of the stimulus intensity on the directional tuning varied by the type of GIs at last year's meeting. This result suggested that encoding of the stimulus direction by GIs is different in its robustness against the stimulus intensity among the cells which play different roles in sensory processing. In addition, the accuracy of direction or velocity encoding for individual and population of cells was analyzed by using cross-validation based on the maximum likelihood estimation method. The stimulus direction was represented by the population activity of three pairs of GIs, which are LGI, GI 10-2, and GI 10-3, whereas the airflow speed was encoded by the cell group consisting of MGI, GI 9-2, and GI 9-3. This result suggests that the stimulus direction and intensity are separately conveyed by different groups of GIs, which may be related to their behavioral functions.

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Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: NIH Grant R01-NS093585

Title: A three-dimensional dynamical model of the rat vibrissal array

Authors: ***N. O. ZWEIFEL**, N. E. BUSH, I. ABRAHAM, T. D. MURPHEY, M. J. Z. HARTMANN;
Northwestern Univ., Evanston, IL

Abstract: The rat vibrissal system is one of the most commonly used models to study how the brain encodes and processes somatosensory information. And yet, methods to accurately predict the three-dimensional (3D) dynamics of rat whiskers and the mechanical signals generated at the base of each vibrissa are still not available. In order to close this gap, we developed a simulation framework that incorporates a realistic 3D model of the full rat whisker array to predict the complete sensory input to the rat vibrissal system. The model for each individual whisker in the array is based on previous work, extending a two-dimensional rigid-link model to three dimensions. The whisker is approximated as a chain of conical frustums connected by equidistant joints with three degrees of freedom, modeled as torsional springs. We optimized the stiffness and damping parameters of the springs such that resonance frequency and damping behavior matched those of a real whisker. Then, we extrapolated the single-whisker model to the full rat whisker array taking into account the typical morphology and whisker geometry across the array. Our simulations show that the motions of the dynamically-optimized whisker model closely match data from real whiskers for multiple trials, achieving Pearson correlation coefficients of 0.91 and 0.94 for horizontal and vertical deflections, respectively. Results from simulation experiments with a single whisker colliding against a straight edge reproduced results from analytical models published in other studies. Resonance experiments with the whiskers of the extrapolated array approximated previous experimental results, validating generalizability of the model across different whisker geometries. Lastly, simulation experiments of the full rat whisker array under various conditions, including passive collisions and active whisking against a peg, demonstrate how the array morphology and the whisker geometry across the array shape the tactile input to the whisker system. Our simulations show that our model approximates the behavior of real whiskers with small error. Thus, we provide a new three-dimensional dynamical model of the rat vibrissa that can accurately simulate the mechanical signals at the whisker base,

including during collisions. In addition, our model generalizes to a full whisker array and provides the means to simulate the complete sensory input to the rat vibrissal system.

Disclosures: **N.O. Zweifel:** None. **N.E. Bush:** None. **I. Abraham:** None. **T.D. Murphey:** None. **M.J.Z. Hartmann:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: NIH R01-NS093585

Title: Simulating deformation of the whisker shaft within the follicle

Authors: *Y. LUO[1], J. W. RUDNICKI[2], M. J. HARTMANN[1,3];
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Abstract: During active whisking behavior, the deformation profile of the vibrissal shaft within the follicle-sinus complex (FSC) is critical to determining the mechanoreceptor response. Current anatomical evidence suggests that the follicle wall is relatively stiff, that the follicle-vibrissal junction is relatively rigid, and that the hair bulb at the base of the vibrissal shaft is relatively soft. A simplified beam-and-spring mechanical model was constructed for the FSC based on this anatomical evidence. The model was validated against an experimental study that measured tissue displacement during passive touch (Whiteley et al., 2015). The model was then used to predict the deformation profile of the vibrissal shaft during active whisking. Results suggest that the vibrissa will pivot around a fulcrum near the follicle entrance, and form a "C-shape" between the level of the ring sinus (RS) and the level of the rete ridge collar (RRC). This C-shape suggests that both RS-Merkel and RRC-Merkel cells will experience similar deformations during whisker deflection. We then modeled the effects of intrinsic muscle activation and the effects of an increase in blood pressure within the RS. The model predicts that both muscle activation and blood pressure increase will enhance the tactile sensitivity of RS-Merkel cells by increasing the static pressure in the tissue within the FSC. We discuss the assumptions required to determine whether this sensitivity enhancement will be biased towards large or small contact deflections. Finally, the model suggests that the deformation profile during active whisking does not qualitatively differ from that during passive touch. This result may allow future qualitative study of mechanoreceptors within the FSC to be conducted during only passive touch (e.g., in the anesthetized animal) and then generalized to active whisking.

Disclosures: **Y. Luo:** None. **J.W. Rudnicki:** None. **M.J. Hartmann:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: NIH R01-NS093585

Title: Complex, three-dimensional whisker stimulation reveals functional tiling of both adaptation and stimulus encoding properties in whisker responsive trigeminal ganglion neurons

Authors: *N. E. BUSH[1], S. A. SOLLA[2], M. J. Z. HARTMANN[3,4];
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Abstract: In order to reveal the full representational capabilities of sensory neurons, it is crucial to observe their responses to a variety of complex and naturalistic stimuli. In the rodent whisker system, mechanical information at the base of the follicle drives the activity of primary sensory neurons in the trigeminal ganglion (Vg). To date, studies of the encoding properties of these neurons have primarily been limited to whisker motion in two-dimensions (2D), often employing restricted stimulus sets. In the present work we quantified the full three-dimensional (3D) shape of whiskers during complex and naturalistic stimulation while recording from Vg neurons. We fit generalized linear models (GLMs) with multiple input filters to predict neural activity in response to mechanical variables at the base of the whisker caused by the 3D deflections. Our results show that individual Vg neurons simultaneously represent multiple mechanical features of a given stimulus, and that rapidly/slowly adapting populations (RA/SA) are not distinct during complex stimulation. When tuning properties of recorded neurons are examined as a population, feature representations are observed to vary continuously and to tile the mechanical stimulus space. Together, these results suggest that Vg neurons employ a distributed code to account for all available mechanical information. Consistent with some earlier studies from the 1960's through the 1980's, as well as some more recent studies, we find that the adaptation properties of Vg neurons do not segregate into clean functional classes.

Disclosures: **N.E. Bush:** None. **S.A. Solla:** None. **M.J.Z. Hartmann:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 485.17/DP06/L3

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: D.04. Somatosensation – Touch

Support: NSF Grant BCS-1734981
NSF GRFP to HME DGE-1324585

Title: Using biomimetic robotic whiskers to simultaneously extract 3D contours and texture: An approach for modeling neural responses in the whisker-trigeminal system

Authors: *Y. YI[1], H. M. EMNETT[1], K. J. KLECZKA[1,2], M. J. Z. HARTMANN[1,2];
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Abstract: We built a robot with artificial whiskers (vibrissae) that can sense 3D contours and textures. The material for the artificial whiskers was carefully chosen to ensure that deformations stay in the elastic regime (i.e., the whiskers do not "kink" or stay deformed after contact). The artificial whiskers are scaled to be either 5x or 10x the size and shape (including taper) of real rat whiskers. The base of each artificial whisker is attached to a robotic "follicle" (a set of sensors) that is designed to measure the mechanical components necessary for accurate 3D contact point extraction. We use the robot to show three results: (1) Consistent with prior work, the 3D whisker-object contact point can be estimated using mechanical signals and their rates of change (time derivatives). This first result is scientifically unsurprising, although it is always exciting to see an algorithm work in hardware. (2) As predicted by simulation, the 3D whisker-object contact point can also be estimated using judicious combinations of the mechanical signals alone, without their time rates of change. This second result holds as long as the whisker is tapered, but does not hold if the whisker is cylindrical. (3) The same whisker can also be used to classify textures based on higher frequency (vibration) signals. Different frequency ranges are used for contour extraction and texture discrimination, so the two can be performed simultaneously. At the same time as we have been building the robot, we have also been performing neurophysiological recordings in the trigeminal ganglion of the real rat. We have developed models for how these (real, biological) neurons respond to mechanical signals at the base of (real, biological) whiskers. We now plan to use the mechanical output from the robot's whiskers as input to the models of neural responses in the trigeminal ganglion. We anticipate that this hybrid robotic/biological approach will ultimately be useful for constraining the kinds of processing that occurs at the level of the brainstem trigeminal nuclei.

Disclosures: **Y. Yi:** None. **H.M. Emnett:** None. **K.J. Kleczka:** None. **M.J.Z. Hartmann:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Topic: D.04. Somatosensation – Touch

Support: NIH Grant R01-NS091439

Title: Coordination of head and whisker kinematics in rats during a three-dimensional tactile search task

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Abstract: Rodents are crepuscular creatures who search and sense their natural tactile surroundings using rhythmic protraction and retractions of their vibrissae arrays (whiskers) in a behavior referred to as “whisking”. The importance of this sensory modality to rodents is accentuated by the expansion of brain areas dedicated to processing whisker mediated information, and by fast sensorimotor loops passing through the rodent trigeminal brainstem nuclei. Whisking behavior is thus widely studied in neuroscience as an excellent model for active sensing and sensorimotor integration. Spatiotemporal control of whisker movements occurs in a complex three-dimensional (3D) world. As rodents burrow, climb, and navigate in their 3D habitats, individual whisks can vary considerably in amplitude and frequency. This exquisite spatiotemporal control of whisking can be seen in the changes in symmetry (a spatial parameter) and synchrony (a temporal parameter) between right and left whisker arrays. Previous studies have shown that the change in symmetry between the left and right whisker arrays is related to the rotational velocity of the head. The degree to which this symmetry is under top-down vs. reflexive control is poorly understood, in part, because most rodent behavior studies utilize either a head-fixed experimental configuration, or behavioral tasks in a planar, two-dimensional (2D) environment (e.g., Y-maze, linear track). We designed a task which employs a naturalistic 3D search behavior. Using recent techniques in machine vision and machine learning, we track head and whisker array position in 3D, exploring the degree to which head/whisker coordination is reflexive versus learning-dependent. We trained rats to stretch from a perch in order to search for a reward within a 3D volume of space, and quantified 3D head position and velocity along with whisker movement. (1) We reconstruct the animal’s head movements in 3D and quantify the effect of head pitch on whisking patterns. (2) We test the effect of modifying the task so that the animal can form a prior expectation of reward location within the 3D volume of space. (3) We

examine the extent to which the animal's learned experience of the environment modifies its tactile exploration strategy so as to maximize its reward. (4) We test whether head velocity and whisking asymmetry coupling is state-dependent and under putative top-down control. This naturalistic 3D task and the kinematic data it generates offers an opportunity to test models of sensorimotor integration. This novel paradigm and methodology can be useful for inactivation studies of sensorimotor structures.

Disclosures: A. Resulaj: None. **K.J. Kleczka:** None. **M.J.Z. Hartmann:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 485.19/L5

Topic: D.04. Somatosensation – Touch

Support: The Barkley Foundation

Title: Cerebral fNIRS hemodynamic response encodes the velocity of patterned tactile stimuli

Authors: *M. HOZAN[1,2,3], J. GREENWOOD[1,2,3], S. M. BARLOW[1,2,3];
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Abstract: BACKGROUND:
The cerebral hemodynamic response (HR) can be non-invasively measured using functional near-infrared spectroscopy (fNIRS) while participants passively receive patterned somatosensory stimulation, or actively perform repetitive motor tasks.
OBJECTIVE:
Whether and to what extent the evoked cerebral HR encodes the velocity of the stimulus pattern when neurotypical adults are presented with paced tactile stimuli at 3 distinct traverse velocities (10, 25 and 45 cm/s) on the dominant glabrous hand.
METHODS:
The fNIRS signal was collected from 11 right-handed neurotypical adults (19-35 yrs, 5F/6M) in two paradigms: passive (sensory) and active (sensorimotor). In the passive task, saltatory pneumotactile stimulation (60 ms pulses, 8-chan) traversed the glabrous hand (D1-D5) at 10, 25 and 45 cm/s. The active paradigm is similarly implemented, except the subjects are asked to perform precision grip at a matching velocity. A randomized block design was used for stimulus presentation (20s stim ON; 20s stim OFF; 10 reps/velocity) during data acquisition (NIRx Scout), [16 dual-tip LED sources (760 nm, 850 nm) and 20 detectors (7.8 Hz sampling rate)] placed bilaterally over motor/somatosensory cortices. HR signals from up to 104 links between sources and emitters were analyzed via the Maximum Likelihood Estimation (MLE) method to

classify the 3 distinct velocities. Common Spatial Pattern (CSP) methodology is used for dimensionality reduction and feature extraction.

RESULTS:

Preliminary results show an average accuracy of nearly 60% in detecting the correct velocity (chance level 33%) when analysis is performed on the raw fNIRS data without preprocessing. The classifier is more accurate in detecting HR features for the lowest (10 cm/s) and the highest (45 cm/s) velocity conditions.

CONCLUSION:

1) Cerebral fNIRS reveals encoding of sensorimotor stimulus features such as saltatory velocity. 2) Methodological differences in the analysis of fNIRS data can lead to different statistical results. Automated algorithms for feature extraction and classification can be beneficial, particularly when there is lack of consensus on signal processing methods.

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Disclosures: M. Hozan: None. **J. Greenwood:** None. **S.M. Barlow:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

Location: Hall A

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Program #/Poster #: 485.20/L6

Topic: D.04. Somatosensation – Touch

Support: NIH/NINDS Grant R01 NS 095251

Title: Does spike timing in somatosensory cortex code for vibratory frequency?

Authors: *T. CALLIER[1], Q. HE[1], S. J. BENSMAIA[2];
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Abstract: Mounting evidence suggests that the precise timing of spikes in cortex plays a role in neural coding. In somatosensory cortex, information about the frequency of skin vibrations has been shown to be carried in both the rates and the timing of the neuronal response. The causal role of spike timing in frequency coding has thus been called into question in this context. To address this ambiguity, we trained monkeys to discriminate the frequency of skin vibrations while simultaneously manipulating stimulus amplitude to decouple rate and timing. Indeed, increases in frequency and increases and amplitude both lead to an increase in firing rate. We also recorded the activity evoked in somatosensory cortex using chronically implanted microelectrode arrays while the animals performed the task. We found that, while firing rate was informative about stimulus frequency at some recording sites, spike timing was informative over a greater proportion of electrodes. When both rate and timing carried frequency information, timing did so more faithfully than did rate. When the two candidate codes - rate and timing -

yielded conflicting signals, the animal's behavior was consistent with the timing code in the vast majority of cases. We conclude that the timing of the response of somatosensory neurons encodes information about vibratory frequency and guides frequency discrimination behavior.

Disclosures: T. callier: None. **Q. He:** None. **S.J. Bensmaia:** None.

Poster

485. Touch: Transduction and Stimulus Encoding

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Program #/Poster #: 485.21/L7

Topic: D.04. Somatosensation – Touch

Support: MRC Grant MR/P006639/1

Title: Sensory and lick-related neuronal activity in mouse somatosensory cortex underlying recognition of elementary tactile sequences

Authors: M. R. BALE, M. BITZIDOU, E. GIUSTO, ***M. MARAVALL**;
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Abstract: Temporal patterning is a key feature of natural signals and is used by the brain to decode stimuli and perceive them as sensory objects. When we hear or touch a sequential stimulus, such as a melody or passage of speech or a texture scanned by our fingertips, the order, timing and context of its concatenated elements are crucial. We sought to dissect how neuronal activity distinguishes between behaviorally relevant sequential patterns.
We developed a GO/NOGO discrimination task in which mice must distinguish between tactile "words" constructed from distinct whisker vibrations assembled in different orders. A sequence or "word" could potentially be recognized through several cues, including the arrival of a specific vibration or the presence of transitions between adjacent vibrations. Adult male mice (n = 30) were trained for several weeks in the task and could reach performance levels > 90%. In this elementary form of sequence recognition, animals sometimes responded to the earliest possible cues allowing discrimination, but enhanced their performance when deliberating for longer (n = 122 sessions, Spearman rho = 0.24, p = 0.0083).
To track the flow of activity during task performance, we optogenetically inactivated cortical regions on interspersed trials, using laser stimulation of inhibitory neurons in VGAT-ChR2 mice (n = 10-11 inactivation sessions per region). Inactivating primary somatosensory "barrel" cortex (S1BF) or secondary somatosensory cortex decreased licking responses in a manner consistent with a loss of sensory input to decision-making stages. Inactivating posterior parietal cortex had no discernible effect. Inactivating primary motor cortex resulted in an increase in licking responses consistent with a motor disinhibition.
Two-photon imaging in layer 2/3 of S1BF and higher areas (n = 7 mice, 31 sessions) revealed

heterogeneous neurons with mixed selectivity to task variables including sensory input, the animal's decision to lick, and the subsequent action and rewards. Neurons selectively responsive to a specific sequence were strikingly rare. In contrast, a large number of neurons, even in primary sensory cortex, were selectively activated preceding goal-directed licking.
These results show that recognition of elementary sequences is cortex-dependent and follows a hierarchical scheme with information flowing serially through somatosensory cortex. Consistent with evidence from other task designs, responses to task variables including licking were plentiful even at the initial cortical stage. These results reveal features of cortical activity that sequence recognition shares with other goal-directed sensory behaviors.

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Poster

485. Touch: Transduction and Stimulus Encoding

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Program #/Poster #: 485.22/L8

Topic: D.04. Somatosensation – Touch

Support: NIH Grant R01NS104928

Title: Rapid sensory adaptation in the thalamocortical network of the mouse and the relative contribution of synaptic depression

Authors: ***N. C. WRIGHT**, P. Y. BORDEN, Y. LIEW, M. F. BOLUS, W. STOY, C. R. FOREST, G. B. STANLEY;
Wallace H Coulter Dept. of Biomed. Engin., Georgia Inst. of Technol., Atlanta, GA

Abstract: Adaptation has been studied extensively in the context of shaping sensory percepts, but the underlying neural mechanisms mediating adaptation remain poorly understood. In the early stages of sensory processing, persistent sensory inputs adapt the thalamocortical network. This phenomenon likely involves a range of mechanisms, including the modulation of thalamic properties such as ongoing and sensory-evoked firing rate, tonic/burst firing, and population synchrony, collectively referred to here as thalamic "state", as well as thalamocortical and intracortical synaptic depression. However, the relative contribution of each remains unclear. Here, we address this question in the whisker pathway of the lightly-anesthetized mouse by obtaining silicon probe and patch clamp recordings in layer 4 (L4) of primary somatosensory cortex (S1), and extracellular recordings in ventral posteromedial (VPm) nucleus of thalamus. We delivered precise punctate whisker stimulus features either in isolation, or embedded in adapting sensory white noise. We found that white noise reduced the amplitude and spatial extent of L4 S1 population feature responses, while reducing theoretical detectability of the whisker deflection and enhancing whisker velocity discriminability. In VPm, sensory white noise

reduced feature-evoked response amplitudes and bursting, suggesting the downstream effects in S1 could primarily reflect changes in thalamic state. Next, we more directly assessed the role of rapid synaptic adaptation at the level of cortex using a transgenic mouse expressing Channelrhodopsin in VPm neurons. We substituted the sensory feature with direct optogenetic stimulation of layer 4 thalamocortical terminals (thus bypassing the effects of thalamic state on the S1 response), and recorded spiking and subthreshold S1 activity. In contrast to sensory feature responses, S1 responses to terminal stimulation exhibited almost no adaptive effects when the stimulus was embedded in sensory white noise. Taken together, these results suggest that the sensory environment may primarily shape cortical responses to embedded sensory features by adapting thalamic firing properties, adding to a growing body of evidence for a more prominent role of thalamic coding than historically thought.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.01/L9

Topic: D.04. Somatosensation – Touch

Support: DFG GO-802/12-1

Title: Effects of transcranial direct current stimulation on tactile perception in musicians and non-musicians

Authors: L. DADASHEV[1], A. A. KARIM[1,2], ***B. GODDE**[1];
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Abstract: Brain plasticity in sensory regions can be facilitated by brain stimulation. The relationship between the magnitude of plasticity and tactile performance with tactile expertise is not yet fully understood. We investigated the effects of transcranial direct current stimulation (tDCS) on tactile perception in tactile experts (musicians) and novices. We hypothesized that anodal, but not cathodal tDCS over contralateral somatosensory cortex would facilitate performance. We further expected these effects would be stronger in experts than in novices. At three separate days, 33 participants (age range: 18-27 years) received 15 minutes of 1 mA anodal, cathodal or sham tDCS in a pseudorandomized design. Pre and post tDCS, tactile sensitivity (Touch Detection Threshold; TDT) and discrimination performance (Grating Orientation Task; GOT) were assessed. Participants were divided into experts (17; semi-professional musicians) and novices (16; no prior instrumental experience). Computer-

typewriting hours per day was assessed as a control variable. In a second analysis, the amount of instrument-playing and computer-typing hours were combined into a 'tactile expertise' variable. Musicians performed marginally better than non-musicians in GOT, only. A significant session by condition interaction effect indicated that only anodal tDCS stimulation facilitated tactile performance. This effect was found for both analysis: with musical expertise as between groups factor and with tactile expertise as continuous covariate. Neither kind of expertise modulated the stimulation effect, but the effect on TDT was stronger in participants with higher baseline performance.

Disclosures: L. Dadashev: None. **A.A. Karim:** None. **B. Godde:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

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Topic: D.04. Somatosensation – Touch

Support: FWO grant 1189817N
KAN FWO grant 1519719N

Title: Inter- and intrahemispheric resting-state functional connectivity alterations associated with upper limb somatosensory recovery early post stroke

Authors: *N. DE BRUYN[1], L. SAENEN[1], L. THIJS[1], E. CEULEMANS[1], S. MEYER[2], K. ALAERTS[1], G. VERHEYDEN[1];
[1]KU Leuven- Neurorehabilitation Sci., Leuven, Belgium; [2]Rehabil. Campus Sint-Ursula, Jessa Hopsital, Herk-de-Stad, Belgium

Abstract: Background: Sensorimotor deficits in the upper limb are present in more than 50% of subacute stroke patients. Knowledge concerning associations of changes in functional connectivity and clinical sensorimotor recovery is warranted. **Aim:** To investigate changes in functional connectivity of the sensorimotor resting-state network associated with clinical recovery of sensorimotor function in the early rehabilitation phase. **Methods:** We recruited 9 subacute stroke patients within 4 months post stroke. Resting-state functional magnetic resonance imaging (rs-fMRI) and a clinical sensorimotor profile was obtained at two time points with four weeks in between, consisting of Perceptual Threshold of Touch (PTT; somatosensory measure) and Stroke Upper Limb Capacity Scale (SULCS; motor activity measure). Three network indices of functional connectivity were created based on individually averaged connectivity values (z-transformed r-values) of a region of interest-to-region of interest analysis: interhemispheric, contralesional intrahemispheric and ipsilesional intrahemispheric index. Non-parametric partial correlations with time since stroke and mean framewise displacement as

nuisance regressors were obtained for the change scores of these three network indices with the clinical recovery scores. **Results:** We included 4 male and 5 female subacute stroke patients with mean age of 64 years (range: 47-79) and mean time post stroke of 82 days (range: 65-113)**.** Somatosensory (PTT) recovery was highly correlated to a decrease in interhemispheric index (r=0.82) and moderately correlated to an increase in contralesional intrahemispheric index (r=-0.53). Motor activity (SULCS) recovery was moderately correlated with an increase in ipsilesional intrahemispheric index (r=0.63). **Conclusion:** Changes in inter-and intrahemispheric connectivity seem to play distinct roles in motor and somatosensory recovery with motor recovery associated with ipsilesional intrahemispheric connectivity alterations and somatosensory recovery linked to inter- and contralesional intrahemispheric connectivity changes. Associations between increased contralesional intrahemispheric connectivity and PTT suggest a supporting role of the contralesional connectivity for somatosensory recovery in early rehab.

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Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.03/L11

Topic: D.04. Somatosensation – Touch

Title: Cortical map remodeling in the intact hemisphere and functional recovery after focal ischemic stroke to the primary somatosensory cortex

Authors: *J. FACCHINI, C. A. XERRI, N. CATZ, Y. ZENNOU-AZOGUI;
Aix-Marseille University, CNRS, Marseille, France

Abstract: After ischemic injury to S1, most studies have focused on the remodeling of perilesional areas and its role in functional recovery. In contrast, consequent alterations within the contralesional cortex remain poorly understood despite its involvement in the functional recovery. Our study investigates in rats the time-course of cortical cutaneous map remodeling in the intact hemisphere following unilateral focal ischemic damage to S1. In parallel, behavioral deficits are assessed to better understand the role of hemispheric interactions in the functional restoration. Using electrophysiological mapping, we explored the post-lesion reorganization of the non-affected forepaw cutaneous representation at several time points during four weeks after the cortical damage induction. We also used behavioral tests assessing tactile sensitivity and sensorimotor coordination. Cortical maps in the intact hemisphere show a representational dedifferentiation inducing a degradation of the somatotopic organization starting from 1 hour and worsening until 14 post-injury days. These changes are underpinned by a dramatic enlargement

of cutaneous receptive fields accompanied with an increase of neuron sensitivity to mechanical stimulation of the skin. Our behavioral observations show a strong impairment of tactile sensitivity and sensorimotor adjustments for the forepaw contralateral to the injured hemisphere, that gradually abated. No impairment was observed for the intact forepaw during behavioral assessments. Interestingly, a substantial, yet incomplete, restoration of somatotopic organization was found to occur at the end of the first postlesion month. This partial restoration appeared to be temporally related to the time course of the functional recovery.These data are in line with the model of lesion-induced alterations of the interhemispheric imbalance, as they are compatible with the transitory decrease of inhibition of the intact cortex originating from the injured side. Our findings underscore the critical role of hemispheric interactions in maintaining a fine somatotopic organization of cutaneous maps in the intact hemisphere and suggest a major implication of the interhemispheric balance in the functional recovery following focal stroke.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.04/L12

Topic: D.04. Somatosensation – Touch

Support: ETH Zürich Postdoctoral Fellowship
Neural Control of Movement lab

Title: Preserved individual finger representations in tetraplegia

Authors: *S. KIKKERT[1,2], M. VERLING[1], D. PFYFFER[2], P. FREUND[2], N. WENDEROTH[1]; [1]Dept. of Hlth. Sci. and Technol., ETH Zürich, Zürich, Switzerland; [2]Spinal Cord Injury Ctr. Balgrist, Univ. of Zürich, Zürich, Switzerland

Abstract: Following spinal cord injury (SCI) or limb amputation, the brain is deprived of sensory input and motor output to the limb(s). Non-human primate studies previously demonstrated that this leads to extensive reorganisation in the primary somatosensory cortex (S1), such that neighbouring body-part representations invade the “deprived” cortex. However, we previously demonstrated that functional representations of amputees’ missing hand are preserved in the “deprived” S1 area, a finding that questions widely held assumptions of brain organisation and reorganisation. Still, since amputees have a relatively intact motor output system (i.e. they can still activate the muscles that used to control the missing limb), it remains unclear how a retained functioning of the motor system contributes to preserving somatotopy. In this study, we used neuroimaging to characterise the somatotopic layout of hands with diminished or absent sensory and motor function in tetraplegic SCI patients.

We used 3T fMRI to investigate whether finger somatotopy is preserved following tetraplegic SCI. We asked 13 chronic cervical SCI patients and matched healthy controls to perform (attempted) individual finger movements in a travelling wave paradigm to uncover finger selectivity. To quantify somatotopic finger representations patterns, we also obtained blocked design data and used representational similarity analysis. To understand which determinants allow sensory representations in S1 to be maintained, we characterised patients' sensory and motor impairments using behavioural measures.
Our preliminary results revealed detailed somatotopy maps of SCI patients' hand, in which neighbouring clusters showed selectivity for neighbouring fingers in contralateral S1, similar to those observed in healthy control participants. This was true even in a patient with complete paralysis and sensory deprivation of the hands. However, inter-finger overlap was increased (i.e. finger separability was diminished) in patients compared to controls, an effect that tended to be more pronounced in patients with greater sensory and motor hand impairments.
Our results show that the functional finger layout of S1 is preserved even if both sensory *and* motor hand function are impaired. Such stable cortical somatotopy suggests that preserved somatotopic representations may be hardwired or maintained through intracortical mechanisms, though they might be shaped further through use-dependent plasticity. Our results further shed light on the determinants that allow sensory representations in S1 to be preserved, which may facilitate the development of individually-tailored neuroprosthetics.

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Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.05/L13

Topic: D.04. Somatosensation – Touch

Title: Somatosensory brain mapping

Authors: *S. LEE[1], M. LEE[1], J. KIM[3], S.-W. PARK[3], J.-H. AHN[3], S. YANG[4], S. YANG[2]; [2]Nano-Bioengineering, [1]Incheon Natl. Univ., Incheon, Korea, Republic of; [3]Yonsei Univ., Seoul, Korea, Republic of; [4]City Univ. of Hong Kong, Kowlong, Hong Kong

Abstract: The shaping and responsiveness of brain map, an indicative of cognitive status, is drastically influenced by experience. Previous representative mapping tools such as penetrating electrodes and magnetic resonance methods have limitation to clinical use largely due to pervasiveness and low spatiotemporal resolution, respectively. Here, our recently develops graphene-based epidural electronics are integrated into an electrocorticography (ECoG) array, therein having a large scale, real-time, and safe recording/stimulation with desirable resolution.

This system is empirically tested for cortical representation of somatosensory maps. Also, electrical stimulation in a subset of graphene spots enables to enhance sensory responses, demonstrating activity-dependent plasticity in a large scale. We propose that this technology heralds a new generation of brain-machine interfaces for studying brain map, map plasticity, and map-related diseases.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.06/L14

Topic: D.04. Somatosensation – Touch

Support: NIH NINDS R01 NS094384-01

Title: Assessing plasticity of somatotopy and receptive field specificity of digit representations in primary somatosensory cortex after injury

Authors: *D. HULSEY[1], J. K. MATHEW[1], M. P. KILGARD[2], S. A. HAYS[3];
[1]Univ. of Texas at Dallas, Richardson, TX; [2]Behavioral and Brain Sci., [3]Bioengineering, Univ. of Texas At Dallas, Richardson, TX

Abstract: Peripheral nerve injuries of the upper limb often result in persistent sensory deficits despite surgical repair. Extensive reinnervation does not ensure functional central organization. Here we study effects of transection and repair of the median and ulnar or radial nerves on S1 representation of the digits in the rat. We use four electromagnetic devices to deliver independent mechanical stimulation of digits 2-5 while recording multiunit activity across the digit region of S1. Using quantitative measure of receptive field specificity and cortical somatotopy, we report extensive disorganization after PNI. We additionally assess effects of pairing vagus nerve stimulation with tactile input on S1 representations. Developing therapies with potential to direct plasticity during reinnervation could help to restore normative cortical and sensory function.

Disclosures: D. Hulsey: None. **M.P. Kilgard:** None. **S.A. Hays:** None. **J.K. Mathew:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.07/L15

Topic: D.04. Somatosensation – Touch

Title: Malleability of the cortical hand map following single digit nerve block

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Abstract: Classical primate studies demonstrate that following single digit amputation, the deprived cortical territory becomes responsive to passive input from its neighbouring digits, demonstrating the capacity of the primary somatosensory cortex (SI) to reorganise. Yet, little research has been carried to characterise the impact of such local reorganisation on the entire hand map, known to comprise of lateral inhibitory circuitry. Here we investigated the malleability of the SI hand map in the acute phase of deprivation. 15 participants attended two 7T MRI scanning sessions (1 mm3 resolution) involving both active and passive stimulation of single digits. ~1 hour prior to one session, participants received a localised pharmacological nerve block of digit 2 (D2). We first used univariate approaches to study digit remapping. D2 activity was significantly decreased in its native territory. Contrary to classical findings, on this short timescale, no significant activity increase was found for the neighbouring digits in the blocked territory, using both passive and active stimulation. Instead, we identified a significant decrease in digit selectivity across the entire hand map with passive stimulation, i.e. in the non-blocked territory. With active stimulation, no selectivity changes were found in the digit map. This indicates that in the acute phase of input loss, activity changes for passive stimulation extend well beyond the deprived cortical region, but additional input associated with the active task can offset this change. To further characterise larger-scale effects to local input loss, we interrogated inter-digit similarity using multivariate pattern analyses, extensively used to characterise human hand representation. We found that both active and passive stimulation resulted in significant reduction of inter-digit dissimilarity, indicating blurring of individuated digit representation, akin to the selectivity reduction mentioned above. However, this collapse in hand structure was also present in the active stimulation condition. Therefore, here we identify more extensive changes to hand representation that cannot be rebalanced with motor input. Our results demonstrate that local deprivation triggers rapid large-scale activity changes, resulting in profound changed to hand representation.

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Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.08/L16

Topic: D.04. Somatosensation – Touch

Support: BCM Seed Funds

Title: Encoding and decoding bimanual vibration frequency information in human sensorimotor cortex

Authors: ***M. RAHMAN**, J. M. YAU;
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Abstract: Vibration frequency perception is a crucial capacity that enables humans to recognize and manipulate objects. While vibration frequency sensing has been extensively studied using behavioral paradigms, little is known about their neural representations in the human brain. Here, we used computational neuroimaging approaches to address two questions. First, how is vibration frequency information - experienced on one hand or both hands simultaneously - represented and combined in the human brain? Second, how do cortical frequency representations differ across different levels of the somatosensory cortical system? We measured and characterized whole-brain BOLD signal changes in participants experiencing a battery of vibrotactile stimulation on their hands. We fitted invertible voxel-wise encoding models to test specific hypotheses regarding population-level vibration frequency tuning and bimanual cue integration. We identified brain regions in parietal and frontal cortex that displayed preferential responses to particular frequency ranges which could be recapitulated by our encoding models which comprised frequency-tuned channels. We inverted the encoding models to successfully decode information about the stimulated hands and vibration frequency from multi-voxel time series patterns. Our findings offer a preliminary view of how bimanual vibration frequency information is represented and integrated in human sensorimotor cortex.

Disclosures: **M. Rahman:** None. **J.M. Yau:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.09/L17

Topic: D.04. Somatosensation – Touch

Support: DARPA, Contract #N66001-10-C-4056

Title: Intracortical microstimulation of bilateral human finger areas of S1 enabled by MRI, fMRI, and intra-operative ECoG mapping

Authors: *M. S. FIFER[1], T. M. THOMAS[2], R. W. NICKL[3], D. CANDREA[2], D. MCMULLEN[7], E. A. POHLMEYER[1], L. E. OSBORN[1], M. C. THOMPSON[8], M. A. ANAYA[4], S. J. BENSMAIA[9], W. SCHELLEKENS[10], N. F. RAMSEY[11], W. S. ANDERSON[5], B. A. WESTER[8], N. E. CRONE[6], P. A. CELNIK[4], G. L. CANTARERO[4], F. V. TENORE[8];
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Abstract: Neuroprosthetic systems remain limited in capability and poorly embodied by users due to their inability to provide naturalistic touch feedback. A long history of work in nonhuman primates has demonstrated that intracortical microstimulation (ICMS) of S1 is able to be reliably perceived. ICMS trains of different amplitudes and frequencies can be discriminated from each other and mapped to mechanical stimuli of varying intensities in a predictable one-to-one fashion. However, the subjective experience of these stimulated perceptions remains poorly understood, since very few human participants have been stimulated in this way. Two previous human S1 ICMS studies have demonstrated a range of cutaneous and proprioceptive perceptions in fingers, forearm, and upper arm.
In this study, one participant with incomplete quadriplegia (including some retained finger sensation) was implanted with three stimulating arrays (Blackrock Microsystems; Salt Lake City, UT) in S1 - two in the dominant (left) hemisphere, one in the non-dominant (right) hemisphere. Preoperative structural and functional MRI imaging were performed and fused into an array placement plan. Intraoperative high-density ECoG (hdECoG) mapping of vibrational fingertip stimulation was performed using custom real-time software to determine placement locations for the stimulating arrays.
At 25 and 35 days post-surgery, our team performed a survey of sensations perceived during ICMS of the implanted electrodes. ICMS was performed electrode-wise at a fixed pulse frequency of 100 Hz with a stimulation amplitude of 60 μA. Stimulation of electrodes in the two

left hemisphere arrays elicited percepts on the right hand ranging in location from thumb to ring finger, from the top of the palm to the fingertip. Stimulation of right hemisphere electrodes elicited percepts predominantly in the left thumb and index fingertip areas. Reported sensations were consistent with both the expected somatotopic gradient of somatosensory representations in postcentral gyrus and the intraoperative ECoG mapping results. The reported finger phalanx of perceived sensation showed a gradient on the two left hemisphere arrays, with percepts closer to the central sulcus being reported as more proximal to the palm. Percepts were predominantly reported as electrical in nature and localized to the palmar side of the hand.
This study further demonstrates the potential for ICMS to provide useful feedback for neuroprosthetic systems. Furthermore, it shows that preoperative imaging and intraoperative ECoG mapping are an effective strategy for targeting sensory array placements for subjects with some retained finger sensations.

Disclosures: **M.S. Fifer:** None. **T.M. Thomas:** None. **R.W. Nickl:** None. **D. Candrea:** None. **D. McMullen:** None. **E.A. Pohlmeyer:** None. **L.E. Osborn:** None. **M.C. Thompson:** None. **M.A. Anaya:** None. **S.J. Bensmaia:** None. **W. Schellekens:** None. **N.F. Ramsey:** None. **W.S. Anderson:** None. **B.A. Wester:** None. **N.E. Crone:** None. **P.A. Celnik:** None. **G.L. Cantarero:** None. **F.V. Tenore:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.10/L18

Topic: D.04. Somatosensation – Touch

Support: DARPA Grant N66001-16-C-4051
NIH Grant 1UH3NS107714
NIH Grant 1U01NS108922

Title: Long-term stability of projected fields evoked via intracortical microstimulation in a human with chronically implanted electrodes

Authors: *V. KARAPETYAN[1], C. HUGHES[1], S. FLESHER[3], M. BONINGER[2], J. L. COLLINGER[2], R. A. GAUNT[2];
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Abstract: The development of sophisticated neural prostheses, which interface directly with the sensorimotor cortex, hold the promise of restoring sensorimotor functions to patients with spinal cord injury or brainstem infarcts, who otherwise have limited options for recovery. Dexterous motor control in healthy individuals relies on intact somatosensory feedback, especially for the

execution of complex tasks. Intracortical microstimulation (ICMS) of the somatosensory cortex is being explored as a means to deliver such sensory feedback in bidirectional neuroprosthetics in hopes of augmenting performance. Animal studies have shown that signal stability of chronically implanted microelectrode arrays may degrade over time due to a multitude of factors. For ICMS to be viable as a feedback source, it must elicit stable sensory percepts in the face of such changes, since failure to do so may result in the need for regular remapping of pulse train parameters and percepts. Studies in nonhuman primates have demonstrated that ICMS thresholds can remain stable over 3 years. However, animal studies are limited in fully characterizing elicited sensory percepts in terms of their quality, location and extent.
In our study, a human participant with a cervical spinal cord injury was implanted with four microelectrode arrays, two in primary motor cortex and two in primary somatosensory cortex. Over the course of 4 years, regular assays were conducted with 100 Hz, 60 μA stimulus trains to characterize the quality, spatial extent, and location of the elicited sensory percepts.
The spatial locations sensory percepts remained stable for the vast majority of electrodes (5.9 ± 3.6 mm spatial drift), with the top 10% most mobile electrodes demonstrating only 13.0 ± 3.1 mm drift. Projected field sizes varied by 28 ± 14%. A small proportion (7/61) of electrodes produced two spatially distinct projected sensory fields over the course of the implant , but once identified, these too remained stable over time.
We demonstrate, in a long-term experiment in humans, that ICMS with microelectrode arrays can generate sensory percepts which remain stable in their size and location over 4 years. This suggests that, even with prolonged use, the electrodes remain functional, and that any movements of the electrode arrays within the cortex that might occur do not meaningfully change the location of the evoked percepts. These results suggest that ICMS could be used as a stable sensory channel in bidirectional brain-computer interfaces.

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Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

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Program #/Poster #: 486.11/L19

Topic: D.04. Somatosensation – Touch

Support: DARPA, Contract #N66001-10-C-4056

Title: Neural responses in human primary somatosensory cortex to vibrotactile stimulation suggest more overlap in afferent representations of individual digits than sensory perceptions elicited by ICMS

Authors: *T. M. THOMAS[1], M. S. FIFER[3], D. N. CANDREA[1], D. P. MCMULLEN[5], R. W. NICKL[2], M. C. THOMPSON[4], E. A. POHLMEYER[4], M. ANAYA[2], G. L. CANTARERO[2], W. S. ANDERSON[6], F. V. TENORE[4], B. A. WESTER[4], P. A. CELNIK[2,7], N. E. CRONE[7];
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Abstract: Intracortical microstimulation (ICMS) is being increasingly studied as a means for restoring tactile perception to patients with spinal cord injuries (SCI). Studies in SCI patients have shown that ICMS in primary somatosensory cortex (S1) can elicit sensations in localized regions of the hand. While the goal of ICMS in SCI patients is to provide sensory feedback during upper-limb neuroprosthetic control using a brain machine interface, the extent to which ICMS can activate native representations of tactile information is still being investigated. In this study, we compared individual finger representations in S1 at the resolution of microelectrode arrays during vibrotactile stimulation of individual digits and during ICMS. A participant with incomplete quadriplegia was implanted with two microelectrode arrays (Neuroport Arrays, Blackrock Microsystems) in dominant S1 (left hemisphere) and one array in non-dominant S1 (right). To guide the placement of arrays, we used electrocorticography (ECoG; 3x21 high-density grid, 3 mm spacing) to record neural responses intra-operatively while vibrotactile stimulation (500 ms) was applied to individual fingertips. During post-recovery sessions, we recorded single and multi-unit activity from the arrays using this same vibrotactile stimuli. We also performed a survey of the sensations perceived while ICMS (100Hz, 60 μA) was applied to individual microelectrode contacts. Surprisingly, somatosensory perceptions elicited by ICMS at individual electrodes were localized to small areas on only one or two digits, even though the same electrodes recorded neural responses from vibrotactile stimulation of up to four digits. Neural responses recorded within each array, however, still presented a somatotopic gradient of the finger representations in agreement with ECoG recordings from the same areas. These findings suggest that somatosensory perceptions elicited by ICMS do not bear a one-to-one relationship to afferent representations of vibrotactile stimuli, and do not simply arise from activation of these representations. Instead, these perceptions may arise from additional processes that select from a subset of activated representations. Further investigation is needed to determine how ICMS-elicited perceptions compare to afferent representations of other sensory modalities, and whether alternate ICMS parameters can elicit perceptions more similar to these native representations. A better understanding of the neural mechanisms responsible for ICMS-elicited perceptions is needed to design effective strategies for providing tactile feedback for neuroprosthetic control.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.12/L20

Topic: D.04. Somatosensation – Touch

Support: Defense Advanced Research Projects Agency N66001-17-C- 4013
Private gift to Arto Nurmikko

Title: Dynamical coupling between primary somatosensory cortex and primary motor cortex during active grasping of a soft compliant object

Authors: *H. G. CU[1], W. TRUCCOLO[2], L. LYNCH[1], K. HUANG[1], D. BORTON[1], A. NURMIKKO[1];
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Abstract: We investigated the neural dynamics underlying the coupling between primary somatosensory (S1) and primary motor (M1) cortices in a non-human primate (Macaca mulatta) during a compliant object grasp discrimination task. Our motivation derives from current state-of-the-art intracortical brain-computer interface (BCI) systems which have allowed tetraplegic patients to control robotic arms and computer keyboards using neural signals from M1 or dorsal premotor cortex (PMd) (Hochberg et al. 2012; Ajiboye et al. 2017). These BCIs currently do not provide tactile sensory feedback as in a closed-loop system capable of sensory-motor integration (Bensmaia and Miller 2014; de Lafuente 2018). The animal was trained on a hand squeeze-and-hold task to actively grasp and maintain a grasping force on a soft rubber manipulandum within a fixed deformation range of the object based on the animal's sensory feedback. After training, we implanted two 96-channels IrOx microelectrode arrays in S1 and M1. For this initial study, we first decoded the softness of object from neural population data alone by calculating the relative similarity between spike trains (SSIMS) (Vargas-Irwin et al. 2015) and applying t-SNE visualization tools to reduce dimension. Then, we classified the different stiffness levels of the object using neural data from either S1 or M1, and from their joint activity. Second, to assess the information flow between these two areas, we applied a Variational Latent Gaussian Process (vLGP) algorithm (Zhao and Park 2017) to infer their low-dimensional dynamics and then computed conditional Granger causality measures, which assess the time causal interaction between these two areas low-dimensional dynamics in both time and frequency domains. We found that combined S1-M1 activity provided the best result in classification, which directly implicates the importance of S1-M1 co-activation in compliant object grasp discrimination. The low-dimensional representations from vLGP captured the overall population neural firing rate in each area and Granger causality indicated a bidirectional coupling between S1-M1. We are currently leveraging these preliminary results, especially the decoding sensory motor dynamics

during controlled grasp of a soft object, to develop new encoding experiments using intracortical patterned microstimulation toward the long term goal of BCIs that incorporate tactile sensory feedback.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Topic: D.04. Somatosensation – Touch

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Title: Task-specific training to promote earlier cortical reactivation and hand use recovery in monkeys after incomplete dorsal column spinal cord injury

Authors: *J. L. REED, H.-X. QI, J. H. KAAS;
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Abstract: After nearly complete unilateral lesions of the dorsal columns (DC) in the cervical spinal cord of monkeys, the deprived hand is greatly impaired and the contralateral somatosensory cortex hand representation is deactivated. However, hand use and considerable reactivation of hand cortex recovers over 5-12 post-lesion weeks. Here, we compare the reactivation of hand cortex in area 3b, as measured with functional magnetic resonance imaging (fMRI), with the recovery of hand use in monkeys with and without task-specific behavioral training. We hypothesized that task-specific behavioral training promotes earlier hand use recovery and functional somatosensory cortex reactivation, detected at approximately the same time after injury. Nine adult male squirrel monkeys (*Saimiri boliviensis*, 4; *S. sciureus*, 5) were randomly assigned to a training or testing group. Monkeys received intensive training on a food pellet retrieval task, or were only tested weekly on the task. Lesions at C4-C6 disrupted some inputs from the digits and palm, while sparing some inputs from digit 1. Time course and extent of cortical reactivations in response to tactile stimulation on the digits were evaluated before DC lesion and 2-3 times post-lesion for 12 weeks with 9.4T fMRI in monkeys under isoflurane anesthesia. Final-stage somatotopic maps of reactivation were compared to patterns of fMRI activation in each monkey. After data collection, brains and spinal cords were processed, and the DC lesions were estimated to range from 60% to 95% complete. Analysts blinded to the conditions processed the fMRI and behavioral data. With generalized linear mixed modeling, we

found an interaction between the DC lesion extent, post-lesion time, and training group contributing to cortical activation, such that greater activation was estimated in the training group monkeys with minor (< 70% complete) lesions for all scan times as early as 2-4 weeks after injury compared to monkeys without training. By 5-6 weeks, greater activation was estimated in the training group across all lesion extents ($p < 0.0001$). Training alone was not a significant factor, while time and DC lesion alone and together tended to affect most measures of hand use and cortical activation. Differences in fMRI signals were modestly correlated with some, but not all, behavioral measures (e.g., grasp time, rho = 0.490, $p < 0.0001$; attempts per successful trial, rho = 0.111, $p = 0.261$). Overall, we found that task-specific training contributes to earlier cortical reactivation and hand use recovery when injuries are incomplete, but cannot overcome all impairments after nearly complete lesions.

Disclosures: **J.L. Reed:** None. **H. Qi:** None. **J.H. Kaas:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

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Topic: D.04. Somatosensation – Touch

Support: BFU2015-66941R (MINECO/FEDER)

Title: Morphometry, topology and structural plasticity in trigeminal nuclei of adult rats exposed to an enriched environment

Authors: *Y. MARTIN[1], C. AVENDANO[2], P. NEGREDO[2];
[1]Francisco De Vitoria Univ. CIF – G80480197, Pozuelo de Alarcon, Spain; [2]Univ. Autonoma de Madrid, Fac. Medicina, Madrid, Spain

Abstract: Brain is able to adapt structurally to changes in the environment even in adulthood. In recent years it has been shown that input- or experience-dependent plasticity is not an exclusive capability of the cerebral cortex, but also occurs at subcortical levels. The trigeminal system of rodents is an excellent substrate to study this type of plasticity. We investigated the morphometry and topology of the dendritic trees of two different populations of primary afferents-targeted trigeminal nuclei neurons, trigeminothalamic 'barrelette' neurons of the principal nucleus (Pr5) and trigeminal intersubnuclear neurons in the caudal division of the spinal trigeminal nucleus that project to the principal nucleus (Sp5c-Pr5). These neurons were retrogradely labeled with dextran amines from injections in the ventral posteromedial nucleus of the thalamus and Pr5, respectively, in controls and after exposing daily the rats to an environmental enrichment (EE) for two months. Fully labeled neurons were digitally reconstructed with Neurolucida and analyzed with NeuroExplorer. In controls, Pr5 neurons showed remarkable side asymmetries in

the number of low-grade trees and the total dendritic length (which was greater on the left side), as previously reported[1]. Sp5C-Pr5 neurons exhibited a more discrete degree of asymmetry mainly consisting of a larger number of spines and shorter distal segments on the right. Exposure to EE neutralized these lateral differences in both neuronal populations, and resulted in a substantial increase in the complexity of dendritic patterns in Pr5 and Sp5c-Pr5 neurons: greater dendritic branching, without total dendritic length increase in Pr5, and increased spatial expansion (as revealed by 3D Sholl analysis) and greater tortuosity of dendrites in Sp5c-Pr5. In the latter, the number of spines also increased, but this increase reached significance only on the left side. In addition, preliminary findings indicate that the changes observed in Pr5 neurons are only partially reversed by returning animals for an additional 2 months to standard housing after EE. These changes could reflect homeostatic processes directed at endowing the system with a convenient structural design that enables an optimal sensory processing when the conditions imposed create a new level of equilibrium.

[1] Negredo et al. (2009) *Neuroscience*, 163.

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Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.15/L23

Topic: D.04. Somatosensation – Touch

Title: VIP neurons receive less ipsi- but more contralateral cortical long-range input in the absence of cortical layers

Authors: *G. HAFNER[1], J. GUY[1], M. WITTE[1], E. M. CALLAWAY[2], J. F. STAIGER[1];
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Abstract: The inhibition exercised by GABAergic neurons is essential for controlling the activity levels of cortical networks. Vasoactive intestinal polypeptide (VIP) expressing inhibitory neurons have received attention as major integrators of long-range input. They exhibit a laminar bias towards the upper cortical layers. We wanted to investigate if their laminar arrangement is a prerequisite to establishing their long-range connectivity. In reeler mutant mice cortical neurons are misplaced and fail to form a laminar organization. We confirmed that VIP neurons lose their typical distribution and are instead equally distributed throughout the cortical thickness. Using rabies virus tracing, we assessed the long-range input sources of VIP neurons in barrel cortex of wildtype and reeler mice. VIP neurons received input from the same areas in both genotypes. The major input sources were other sensory cortices, motor cortex, posterior parietal association area, and the thalamus. The proportion of subcortical input was preserved in reeler, which indicates that the malpositioning of VIP cells does not hinder their capacity to receive long-range

input per se. However, VIP neurons in reeler mice received a much lower number of ipsilateral cortical inputs and a much higher number of contralateral cortical inputs. We hypothesize that the disorganized arrangement of neurons in reeler compromises the establishment of cell-type specific ipsilateral long-range projections and necessitates compensation by an excess of contralateral inputs. Based on our results we argue that in the absence of a laminar structure, VIP neurons are still maintaining their connectivity with subcortical structures while their cortical connectivity is fundamentally altered.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Topic: D.04. Somatosensation – Touch

Support: JCYJ20180507182458694
EMBO LTF 853-2017
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BMBF 01GQ1001A

Title: Structural and functional seasonal plasticity in layer 4 of the adult somatosensory cortex

Authors: *S. RAY[1,2], **M. LI**[3], S. MUELLER[4], P. BOEHM-STURM[4], M. BRECHT[2], R. K. NAUMANN[3];
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Abstract: Seasonal cycles govern life on earth, from setting the time for the mating season to influencing migrations and governing extraordinary physiological conditions like hibernation. Brain volume and cortical thickness which change over long time scales are among the most commonly used markers of human structural brain plasticity, but their effects on neuronal activity remain unknown. The study of functional neural plasticity has largely been performed in rodents and been limited to changes in synaptic connections or synaptic weights at very short time scales. Among mammals, shrews are known to show striking seasonal plasticity in skull and brain sizes and thus afford a unique opportunity to identify the functional changes in neuronal activity caused by long term structural brain plasticity. Here we show that the Etruscan shrew, the smallest terrestrial mammal, shows large, correlated seasonal variation in brain structure and function. We find reversible changes in the volume of the cortex, with the volume decreasing

from summer to winter and investigate changes related to the shrew's most important sense - touch - in greater detail. The somatosensory cortex undergoes a layer specific shrinkage during winter that is most pronounced in layer 4, which shrinks by ~30%. This decrease in thickness is linked to a similar reduction in the number of cells in layer 4 of somatosensory cortex. We perform functional two-photon imaging across multiple cortical layers, which revealed a lower number of neurons being suppressed on whisker stimulation during winter. This effect is most prominent in layer 4 of somatosensory cortex with less than half the neurons being suppressed on touch during winter compared to summer. The decrease in the neuronal suppression on touch in winter is accompanied by a reduction in the number of PV+ interneurons and WFA+ perineuronal nets that structure inhibition. The resulting inhibitory tone may adapt the balance for detecting sensory stimuli - and prey - during the cold season, enabling the shrew to be less particular in its choice of food. Informal observations from capture attempts suggest that shrew population density is low in winter and spring and higher in summer and fall, perhaps indicating an annual variation in resource availability and survival. Varying the food resources in the laboratory, also leads to a selective shrinking of the cerebral cortex. Taken together, our findings suggest that Etruscan shrews sacrifice early sensory cortical processing and inhibitory sensory gating in order to survive winter.

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Poster

486. Touch: Cortical Encoding and Plasticity

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Program #/Poster #: 486.17/L25

Topic: D.04. Somatosensation – Touch

Support: NIH Grant 5R01HD084362-04

Title: The organization of somatosensory cortex in prairie voles (Microtus ochrogaster): Do parental rearing styles impact the functional organization of somatosensory cortex?

Authors: C. R. PINEDA[1,2], M. K. L. BALDWIN[2], ***L. A. KRUBITZER**[1,2];
[1]Psychology, [2]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA

Abstract: Early life experience can have a dramatic effect on the functional and architectonic organization of the neocortex. The effects of early sensory input on brain development has been demonstrated by our laboratory in multiple animal models using loss of visual inputs via bilateral enucleation, and differential rearing conditions. We continue to explore how early life experience alters the functional organization of cortical fields in the prairie vole (*Microtus ochrogaster*), taking advantage of their monogamy, biparental nature and their natural variation in rearing

style. Parent-pup interactions include huddling, licking and nuzzling involving prolonged perioral contact. Therefore, we can examine the functional organization of somatosensory cortex in offspring that were exposed to extremes in their tactile interactions with their parents. In several related studies these offspring have been termed high (HC) and low contact (LC). These different parental rearing styles result in behavioral differences in the offspring, independent of genetic inheritance, as shown by cross-fostering studies. Our laboratory has demonstrated that HC and LC offspring have differences in the cortical connections of the perioral representation in the primary somatosensory cortex (S1). Additionally, HC and LC offspring have differences in the relative size of the primary sensory areas in the neocortex. In the current investigation we examine the effect of natural variations in early sensory input delivered to the offspring through their parents (HC vs. LC) on the functional organization of S1. We use previously demonstrated behavioral quantification techniques to produce low contact and high contact prairie voles. Once these animals reach adulthood, we use multiunit electrophysiological recording techniques to characterize the topographical map of S1, with an emphasis on the representations of ethologically important anatomical structures, such as the snout and vibrissae. These data contribute to a growing literature on the mechanisms of intergenerational transmission of behavioral adaptations, independent of genetic inheritance.

Disclosures: **C.R. Pineda:** None. **M.K.L. Baldwin:** None. **L.A. Krubitzer:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.18/L26

Topic: D.04. Somatosensation – Touch

Support: NIH R01-NS088958
NIH F30-MH118865
BrainHub Presidential Fellowship, Carnegie Mellon University

Title: Rewarded sensory experience persistently increases excitatory connectivity in superficial layers of somatosensory cortex

Authors: *S. E. MYAL, A. L. BARTH;
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Abstract: Pyramidal neurons in Layer 2 (L2 Pyr neurons) are well-suited to integrate task-relevant sensory information, as they integrate input from within and outside the cortical column and their connectivity can reflect co-active, feature-specific neural ensembles that can change with imbalanced sensory input. We sought to test whether naturalistic sensory stimulation could induce changes in L2 Pyr-to-Pyr connectivity, and whether these changes could be enhanced

with sensory-reward association training. To compare the effects of uncoupled versus reward-associated sensory stimulation, we used an automated home-cage training system in which mice (C57BL/6, 19-28 days old) nosepoke to receive a water reward accompanied by a gentle air puff onto the right whisker pad. Mice were not water deprived and all trials were self-initiated. After 24 hours of reward-uncoupled whisker stimulation, paired whole-cell recordings of L2 Pyr neurons from contralateral S1 barrel cortex were done to assess changes in synapse function. We found that 24-hour stimulation doubled connectivity rates and increased the number of bidirectional synapses between L2 Pyr neurons. Amplitude, failure rate and paired-pulse ratio were unchanged from baseline, suggesting new synaptic connections were not detected because of enhanced presynaptic release. However, the increase in L2 Pyr connectivity was transient and normalized after 5-day stimulation. We next assessed the effects of sensory-reward association training (SAT, in which whisker stimulation is coupled to water reward). SAT for 24 hours also doubled L2 Pyr connectivity and did not alter presynaptic release properties. In contrast to reward-uncoupled whisker stimulation, Pyr connectivity remained high after 5-day SAT. Thus, we find that L2 Pyr connectivity in S1 can be rapidly altered by naturalistic sensory stimuli, and that L2 circuits differentiate between reward-coupled and reward-neutral sensory inputs. These results challenge the notion that long-lasting, context-dependent plasticity is restricted to higher-order sensory cortical areas and suggest that task-relevant, rewarded sensory information activates distinct cellular and molecular pathways that regulate the persistence of cortical neural ensembles.

Disclosures: **S.E. Myal:** None. **A.L. Barth:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.19/L27

Topic: D.04. Somatosensation – Touch

Support: NIH R01 NS096971

Title: Trunk cortex is a sensorimotor amalgam

Authors: ***F. P. PAUZIN**[1], B. NANDAKUMAR[2], G. H. BLUMENTHAL[1], K. A. MOXON[1]; [1]UC Davis, Davis, CA; [2]Univ. Of California Davis, Davis, CA

Abstract: Sensorimotor integration is crucial for perception and volitional movement. Understanding the substrates of sensorimotor integration is important for studies examining learning and recovery after neurological injury or disease, yet little is known about the details of the trunk sensorimotor system. To investigate trunk cortex sensorimotor integration, we used the rat sensorimotor trunk regions of the cortex to address four main goals. First, to identify the

extend of reorganization within trunk cortex, single neuron sensory mapping was used. Second, to similarly identify the extent and internal organization of the trunk motor cortex, intracortical microsimulation (ICMS) was used. Third, to assess sensorimotor integration, sensory evoked potentials were compared across a broad region of sensorimotor cortex. The electrophysiological assessment of the trunk sensorimotor system revealed a surprising amount of somatotopy within the trunk sensory and motor cortices with integration between them. Fourth, high intensity sensory stimuli, which likely activates both proprioceptive and noxious pathways, is highly integrated between hindlimb and trunk sensorimotor cortices but not forelimb. Interestingly, this high intensity stimulation of the hindlimb leads to a stronger response in trunk primary motor cortex (M1-trunk) than the same intensity of stimulation to the trunk itself.
To determine if this cross modality activation to M1-trunk is due to outnumbering projections from primary somatosensory hindlimb cortex (S1-hindlimb) compared to S1-trunk, fluorescent latex microspheres were used as a retrograde neuronal tracer and injected into M1-trunk as determined by the ICMS motor mapping. Interestingly, an equal number of cells from S1-hindlimb and S1-trunk projected to M1-trunk, confirming that M1 trunk is a crossroad in sensorimotor integration. Most of the projecting sensory neurons were found in layer 5 and layer 2/3 of both sensory cortices. However, many cells projecting to M1-trunk were of thalamic origin suggesting that the cross modality activation may have a thalamic provenance. This thalamic projection may be the source of stronger HL activation of M1-trunk compared to trunk activation of M1-trunk. Alternatively, the stronger response in M1-trunk from HL sensory stimulation may be due to a difference in the cortico-cortical projection's strength (analyses are still in preparation). These data fill a gap in our understanding of trunk motor cortex and make clear that its organization supports its functional role.

Disclosures: F.P. Pauzin: None. **B. Nandakumar:** None. **G.H. Blumenthal:** None. **K.A. Moxon:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.20/L28

Topic: D.04. Somatosensation – Touch

Support: NIH Grant R01-NS091439

Title: Responses of neurons in spinal trigeminal nucleus interpolaris (SpVi) to stimulation of the whiskers in different directions and at different speeds

Authors: *T. J. ALSTON[1], C. S. BREESE[2,1], K. J. KLECZKA[1], A. RESULAJ[1], M. J. Z. HARTMANN[1];
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Abstract: An important open question in the study of somatosensation is how animals integrate signals from an array of spatially distributed tactile sensors. The present study seeks to address how spatial information is integrated across sensors at the earliest stage of the somatosensory system, using the rat whisker (vibrissal) array as a model. Rats have approximately 30 whiskers on each side of their face arranged in an orderly array of rows and columns. The base of each whisker is embedded within a follicle filled with mechanoreceptors that send signals to primary sensory neurons in the trigeminal ganglion. From there, information is sent to several nuclei in the trigeminal brainstem, including spinal trigeminal nucleus interpolaris (SpVi). Neurons in SpVi have been shown to integrate inputs from multiple whiskers(Furuta 2010). One recent study suggested that SpVi may encode information about the speed and direction of a stimulus moving through the whisker array (Kaloti 2016). However, hardware constraints limited whisker stimulation to the rostral-caudal direction. The present experiments use a novel multi-direction stimulation device to further test the hypothesis that neurons in SpVi encode information about both stimulus direction and speed. We designed and built a stimulator that can mechanically stimulate whiskers in any direction and with a range of speeds mimicking natural tactile interactions. Importantly, we show that the stimulator can also detect whisker contacts as it passes through the array. Using this novel stimulation technique, we performed recordings from a set of SpVi neurons in anesthetized rats. Preliminary data reveal clear differences in spike rates associated with different stimulation speeds and directions, showing tuning of these recorded neurons to object orientation and passing speed through the array. We expect these results to improve our understanding of how spatial information is processed and encoded in more central structures of the somatosensory pathway.

Disclosures: T.J. Alston: None. **C.S. Breese:** None. **K.J. Kleczka:** None. **A. Resulaj:** None. **M.J.Z. Hartmann:** None.

Poster

486. Touch: Cortical Encoding and Plasticity

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 486.21/L29

Topic: D.04. Somatosensation – Touch

Support: NIH R01-NS091439

Title: Automated markerless tracking of the vibrissal array and 3D head pose of rodents during a search task

Authors: *K. J. KLECZKA[1,2], A. RESULAJ[3], M. J. Z. HARTMANN[1,2];
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Abstract: The rodent vibrissal (whisker) system is a commonly used model in sensorimotor studies, but our ability to fully characterize the way in which rats and mice use their whiskers during natural behaviors is limited. Manual tracking of video data is time consuming, and automated tracking often requires invasive markers to be placed on the animal, or requires the motion or behavior of the animal to be artificially restricted. Using a combination of publicly available tools and custom written code, we developed a method to extract 3D head pose and position of rats and mice, as well as average vibrissal array protraction angle and spread, while animals performed a search task. Three high speed cameras recorded a perched animal searching for a reward in 3D space. A multi-camera calibration was performed, and DeepLabCut (Mathis et al. 2018) was used to track key points on the head and whisker arrays for each camera view to create a 3D representation of the head and whisker arrays. These data can then be compared with a simulated rat head and whisker array to determine the most likely array configuration. The results of the automated tracking were comparable to a small subset of manually tracked video.
Mathis A., Mamidanna P., Cury K.M., Abe T., Murthy V.N., Mathis M.W., and Bethge M. (2018) Deeplabcut: Markerless pose estimation of user-defined body parts with deep learning. Nature Neuroscience. 21(9): p. 1281-1289.

Disclosures: K.J. Kleczka: None. **A. Resulaj:** None. **M.J.Z. Hartmann:** None.

Poster

487. Scenes and Space

Location: Hall A

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Program #/Poster #: 487.01/L30

Topic: D.07. Vision

Support: NIH R01 EY023384
NSF IIS-1822683

Title: Evidence for visual representation of numerosity in natural scenes

Authors: *M. MELL[1], G. ST-YVES[1], E. J. ALLEN[2], Y. WU[3], K. N. KAY[4], T. NASELARIS[1]; [1]Neurosciences, Med. Univ. of South Carolina, Charleston, SC; [2]Psychology, [4]Radiology, [3]Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: In visual cortex of human and non-human primates, high-level visual areas near intraparietal sulcus have been shown to explicitly encode the number of objects in visual displays. To date, evidence for this numerosity code has come from experiments that use simple dot-like visual stimuli, raising the question of whether the numerosity code persists during perception of natural scenes. Here, we assessed evidence for a numerosity code in high-resolution fMRI measurements of responses to thousands of natural scenes in 8 human subjects. To test for numerosity coding we constructed an encoding model that predicted voxelwise

responses as a function of local object counts in each natural scene. We found that a model based upon local object counts was able to accurately predict voxelwise activity in visual cortex. To test if local object counts were acting as a proxy for simple low-level image features, we constructed voxelwise encoding models based on Gabor wavelet filtering of the natural scenes. For voxels in anterior visual cortex, the numerosity encoding model generated more accurate predictions than the Gabor model, indicating that the numerosity code is computationally distinct from low-level visual features. Our results offer evidence for a numerosity code in anterior visual cortex during natural scene stimulation, and suggest that numerosity may be a key higher-order feature that is extracted by the brain during perception of natural scenes. Recent studies have suggested deep convolutional neural networks trained for object classification may include numerosity as an emergent property; further analyses of our data will be directed towards assessing to what extent the computation of numerosity in these networks is similar to that used by the brain.

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Poster

487. Scenes and Space

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Topic: D.07. Vision

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S10 RR026783 “Multichannel Transmit Frontend for 7 Tesla”
WM KECK Foundation
1S10OD017974-01 “High Performance Connectome Upgrade for Human 3T MR Scanner”

Title: The natural scenes dataset: Massive, high-quality whole-brain 7T fMRI measurements during visual perception and memory

Authors: *E. J. ALLEN[1], Y. WU[1], J. HUTCHINSON[2], T. NASELARIS[3], K. N. KAY[4]; [1]Univ. of Minnesota, Minneapolis, MN; [2]Dept. of Psychology, Univ. of Oregon, Eugene, OR; [3]Neurosciences, Med. Univ. of South Carolina, Charleston, SC; [4]Radiology, Univ. of Minnesota Twin Cities, Minneapolis, MN

Abstract: In order to improve models of visual information processing, high-quality datasets are critical. We are conducting a large-scale ultra-high-field fMRI experiment (7T, whole-brain, T2*-weighted gradient-echo EPI, 1.8-mm resolution, 1.6-s TR) in which 8 exemplary human

participants view many thousands of color natural scenes over the course of 40 scan sessions over the span of a year. As subjects fixate a central point, they perform a long-term continuous recognition task in which they judge whether they have seen each image at any time during the experiment, either in the current scan session or any previous scan session. Initial analyses indicate that the data are of exceptional quality, with subjects having nearly perfect response rates, high task performance, low head motion, and spatially stable brain imaging across scan sessions. Further, across repeated trials of the same image, brain activity patterns are highly replicable. High-quality anatomical data including multiple T1s, T2s, diffusion imaging, angiograms, and venograms have also been acquired. Both raw and pre-processed data will be made freely available to the scientific community, and could be used to develop and benchmark computational models as well as help answer a multitude of neuroscientific questions.

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Poster

487. Scenes and Space

Location: Hall A

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Program #/Poster #: 487.03/L32

Topic: D.07. Vision

Support: NIH Grant R01EY022443

Title: Natural scene statistics of depth and motion pertinent to figure-ground segregation

Authors: X. HUANG[1], C. WANG[1], B. ARSENEAU[1], T. E. YERXA[2], *E. A. COOPER[3]; [1]Dept. of Neuroscience, Sch. of Med. and Publ. Hlth., Univ. of Wisconsin – Madison, Madison, WI; [2]Sch. of Optometry, [3]Sch. of Optometry & Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA

Abstract: Segmenting objects from visual scenes, known as figure-ground segregation, is a fundamental function of vision. To examine the neural computations underlying figure-ground segregation, we previously investigated how neurons in the middle-temporal (MT) cortex of macaque monkeys—a cortical area important for motion and depth processing—segregate overlapping visual stimuli. Based on this work, we hypothesized that the properties of MT neurons in response to the binocular disparities and retinal motion of multiple stimuli might reflect a strategy to achieve figure-ground segregation that exploits statistical regularities in these cues during natural vision. To test this hypothesis, it is important to understand the properties of figure and ground during natural vision within spatial regions comparable to the receptive fields (RFs) of cortical neurons. Here, we present the results of a simulation aimed to address this question for foveal and parafoveal MT. First, natural scenes were drawn from an existing dataset

containing both luminance images and high-precision depth measurements (Burge, McCann & Geisler 2016). To label figure and ground regions, human subjects were instructed to identify and trace the boundaries of salient objects in the scenes when they viewed only the luminance images. Next, we placed a simulated observer in each 3D scene. We selected binocular fixation points at random as well as the speed and direction of observer motion, assuming the observer maintains fixation while moving. We then selected a set of random locations for simulated MT RFs (diameter equal to eccentricity) and calculated the distances, binocular disparities, and speeds of points falling within each RF. We found that the average distribution of distances within RFs was bimodal with peaks at near and far depth planes, suggesting that it is common to have multiple surfaces at different depths present within individual neurons' RFs during natural vision. Zeroing in on the RFs falling at the border between figure and ground regions, we found that figure regions tended to be associated with nearer binocular disparities, both in the absolute sense, and relative to the ground regions. Figure and ground regions also tended to differ in speed generated by self-motion, but not as systematically as disparity. However, when isolated objects move in the world, the figure-ground speed difference is likely to be greater. Our results reveal statistical patterns of figure versus ground regions in natural vision, which will guide future studies to determine whether neurons in primate visual cortex exploit these patterns to aid in the segmentation of objects in cluttered natural environments.

Disclosures: X. Huang: None. **C. Wang:** None. **B. Arseneau:** None. **T.E. Yerxa:** None. **E.A. Cooper:** None.

Poster

487. Scenes and Space

Location: Hall A

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Topic: D.07. Vision

Support: NEI R01EY026042 to SP
National Research Foundation of Korea (NRF) grant (funded by MSIP-2019028919) to SP

Title: Neural representation of obstacles in a scene

Authors: *Y. LEE, S. PARK;
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Abstract: Among many interactions we have with objects in the visual world, perceiving and avoiding obstacle objects on our pathway is crucial. What makes an obstacle? An obstacle perception comes from representing spatial relationship of two essential local elements in a scene—an object and a visual path. If a non-portable object (e.g., large furniture) lies in the

middle of the path, it serves as an obstacle, as compared to when it lies clearly out of the path. Previous research using human fMRI has reported that the Parahippocampal Place Area (PPA) is sensitive to subtle changes in the spatial relationship of local elements, while the Occipital Place Area (OPA) is insensitive to such changes and rather represents the number of local elements. Here, we test whether the PPA shows sensitivity to the presence of an obstacle in a scene. Four types of scenes were tested: object only (a large, less portable object in a blank background), path only (a scene with an empty path), object-out-path (a scene with an object located outside of the path), object-in-path (a scene with an object inside the path). Even though the number of local elements are equal between object-out-path and object-in-path conditions, only the latter contains an obstacle. In an event-related design, participants (N = 8) viewed these scenes while performing a color dot matching task on two dots laid over scenes. Using a Representational Similarity Analysis (RSA), we constructed two simple model RDMs: 1) obstacle model (object-in-path vs. others); 2) number of local elements model (one local element (object only; path only) vs. two local elements (object-out-path; object-in-path)). The RSA revealed a significant correlation (Kendall's tau-a) between the neural RDMs for the PPA and the obstacle model, but not local elements model. On the contrary, the neural RDMs for the OPA showed high correlation with both models. These preliminary results indicate that the PPA is sensitive to presence of an obstacle in a scene, created by a meaningful object-path relationship. This suggest that the PPA may play a role in representing the navigational affordance of a scene based on the relationship between object and spatial boundary elements of a scene.

Disclosures: **Y. Lee:** None. **S. Park:** None.

Poster

487. Scenes and Space

Location: Hall A

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Program #/Poster #: 487.05/L34

Topic: D.07. Vision

Title: Predictive models of neural activity in response to natural stimuli from large scale physiology

Authors: M. D. OLIVER[1], B. HU[2], D. MILLMAN[3], X. JIA[4], D. J. DENMAN[2], J. H. SIEGLE[1], S. R. OLSEN[2], S. E. DEVRIES[2], S. MIHALAS[2], ***M. A. BUICE**[2];
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Abstract: Building accurate predictive models of neural activity is a central goal of visual neuroscience. However, creating such models is exceedingly difficult due to the large potential space of inputs and the nonlinear response properties of neurons. In optical physiology, the recorded responses are also often exceptionally sparse, with an average event rate of ~0.2 Hz. To

overcome these obstacles, we seek to observe responses to an extremely large stimulus set dense in natural features and use this data to fit a variety of predictive models. We use optical physiology to record from the visual cortex of mice, aggregating data by matching cells over up to nine recording sessions. Each recording session contains 50 minutes of "training" stimuli consisting of previously unseen natural movie clips, each between 1 and 10 seconds in length, randomly sampled from a variety of sources. Each recording session also contains ~20 minutes of "validation" stimuli. The "validation" stimuli are the same in each recording session and consistent of a fixed sequence repeated 20 times. We fit a variety of models to the "training" data for each neuron, including linear, quadratic, sparse wavelet and convolutional neural network models. Importantly, each of these models is designed to capture the full spatio-temporal receptive field of each neuron, rather than just their spatial tuning properties. We find that of the models, the convolutional neural network model exhibits the best generalization performance. Furthermore, we find that generalization performance is greatly dependent upon the amount of training data available for each neuron. Finally, we use the trained convolutional neural network models to provide visualizations of neural tuning properties throughout mouse visual cortex.

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Poster

487. Scenes and Space

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Support: RO1-EY25670 to ML
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F31EY027201 to JG

Title: Sulcal depth is a marker for the development and evolution of scene selectivity in high-level visual cortex

Authors: *K. S. WEINER[1], V. S. NATU[2], M. J. ARCARO[3], M. A. BARNETT[4], J. GOMEZ[1], M. S. LIVINGSTONE[3], K. GRILL-SPECTOR[5];
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Abstract: Sulcal pits (SPs) are the deepest points along sulci and are genetically and behaviorally relevant. However, the relationship between functional regions and SPs across human development and evolution remains untested. Here, we fill this gap in knowledge by investigating this relationship in a target region that (a) shows selective neural responses for visual presentations of places and scenes and (b) is located deep within sulci in both macaque and human ventral temporal cortex (VTC). Using functional and structural MRI, we identified place-selective regions and sulcal depth maps in 9 macaques, 26 children (5-12 years old, yo), and 28 adults (22-28 yo). Across ages and primate species, we evaluated (a) the anatomical-functional correspondence between place-selectivity and sulcal depth and (b) if cortical surface properties show developmental or evolutionary variations. Our analyses revealed six main findings. First, the topological location of the SPs along the length of the relevant sulcus overlaps with the functional place-selective region, in each species. Second, the place-selective SPs in VTC are ~2.8 times deeper in humans compared to macaques (main effect of species in a 2-way Analysis of variance (ANOVA) with factors species (human/macaque) and hemisphere (left/right): $F_{1,122}$=531.65, p<0.001). Third, place-selective SPs are ~1.1 times deeper in adults than children (main effect of age in a 2-way ANOVA with factors age of subject (child/adult) and hemisphere (left/right): $F_{1,104}$=15.59, p<0.001). Fourth, calculating the correlation between place-selectivity and sulcal depth revealed a significant positive correlation across age groups and species (adults(R±sem):.52±.07; children: 38±.07; macaques: .40±.1). Fifth, this correlation was stronger for human adults than children ($F_{1,104}$=5.12, p<0.05). Sixth, a model of sulcal deepening indicates that differential local properties that are intrinsic to the cortical surface may explain the morphological changes observed in place-selective sulci across species. Together, these findings support a novel hypothesis that the deepening of SPs is an anatomical feature that may reflect the development and evolution of scene-selectivity in high-level visual cortex.

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Poster

487. Scenes and Space

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 487.07/L36

Topic: D.07. Vision

Title: Expanding visual feature spaces towards a general encoding model of scene perception

Authors: A. Y. WANG[1], M. J. TARR[2], L. WEHBE[3];
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Abstract: Encoding models are widely used in understanding feedforward information processing in human perception. These models have achieved some success in predicting lower-level visual cortex responses in humans and primates using features that were learned via a convolution neural network trained on object recognition. However, higher-level neural responses for scene processing have, as of yet, not been well accounted for by such models. More generally, it is unknown what higher-order features are fundamental for scene perception. In order to exploit the power provided by encoding models to explain basis of scene perception, we created feature spaces that comprehensively captures the kinds of information used in biological scene processing. Feature spaces included activations from pretrained convolutional neural networks, latent feature spaces that are shared by 20 different low and mid level computer vision tasks, such as surface normals and 3d euclidean distances, as well as scene semantics and contextual properties of scenes that are extracted using techniques from language models. BOLD5000, a large-scale fMRI dataset using 5000 images was used to explore the efficacy of these features. During the experiment, four subjects are presented with scene images from standard computer vision datasets (ImageNet, COCO, and SUN) and asked to give a valence judgement. Consistent with previous results, features extracted from convolutional neural network activations of the images explained significant variance of brain responses. Activations from late convolutional layers predicted more anterior parts of the brain including scene regions (PPA, OPA, RSC, etc), while activations from earlier layers predicted early visual cortex. Our results further showed that the computer vision task on which the features are based is critical for predicting brain responses. Features from 3D tasks such as 3D keypoints and 3D edges explained higher variance of the data compared to 2D ones in both regions of interest and voxels from the whole brain. Semantic features of images that are extracted from embedding models of text corpus and image corpus also predicted posterior parts of the cortex. Modern computer vision algorithms thus provide a rich set of tools to represent different types of visual information and enable us to build increasingly general models of scene perception.

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Poster

487. Scenes and Space

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Topic: D.07. Vision

Support: DBT-Wellcome India Alliance (Grant # IA/S/17/1/503081)

Title: How we recognize patterns on crumpled surfaces

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Abstract: When we see a crumpled dress with polka dots, we easily infer that the dots are circular. But whether our visual system automatically recovers patterns from crumpled surfaces is unknown. To investigate this possibility, we created stimuli in which patterns are superimposed on surfaces. Critically, the pattern could be either flat or crumpled independently of the surface being flat or crumpled. We hypothesized that the perceived dissimilarity between congruent stimuli (in which both pattern and surface undergo identical distortions) would be smaller than for incongruent stimuli (in which the pattern and surface undergo opposite distortions). Thus, a straight line on a flat surface would appear similar to a bent line on a bent surface. To measure perceived dissimilarity we asked subjects to search for an oddball target among distractors.

We performed three experiments on human subjects to test this hypothesis. In Experiment 1, we sought to characterize how pattern and surface shape combine in perception. To this end, we asked subjects to search for targets that differed from its distractors either by a pattern change, surface change or both. This revealed that the net dissimilarity between two such stimuli was a linear sum of the dissimilarity due to pattern change and due to surface change. However we did not detect any difference between congruent and incongruent pairs.

In Experiment 2, subjects were asked to search for a target among multiple identical distractors, and we asked whether search was easier with congruent or incongruent distractors. This revealed a systematic difference: searching for congruent distractors was significantly faster, suggesting that the two distractors were more similar, confirming our hypothesis. However, this result was based on testing simple patterns (E, H, Y etc) superimposed on simple surface changes related through bending or rotation. In Experiments 3 & 4, we tested the generality of these results. In Experiment 3, we tested simple patterns on complex surfaces such as bumps, saddles, ripples and arbitrary crumpling. In Experiment 4, we tested complex patterns such as object silhouettes on complex surfaces. Across all experiments, congruent stimuli were found to be more similar than incongruent stimuli.

Taken together, our results demonstrate a novel form of invariance in our perception that allows us to recognize patterns on crumpled surfaces.

Disclosures: P. Gangopadhyay: None. **S.P. Arun:** None.

Poster

487. Scenes and Space

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 487.09/L38

Topic: D.07. Vision

Support: NSERC
BrainsCAN
NSERC Create

Title: Real-world physical distance drives human fMRI activation throughout the visual hierarchy

Authors: *M. MALTSEVA[1], D. J. QUINLAN[2], K. M. STUBBS[3], T. A. KONKLE[4], J. C. CULHAM[1];
[1]Dept. of Psychology, [2]Psychology, Huron Col., [3]Western Univ., London, ON, Canada; [4]Psychology Dept, Harvard Univ., Cambridge, MA

Abstract: The brain transforms 2D retinal information into estimates of physical size and distance based on pictorial and binocular cues. Many studies on these factors have relied on images where they must be inferred and have studied factors in isolation. We investigated how brain activation levels (and patterns) in ventral- and dorsal-stream regions depend upon multiple factors that naturally co-occur: retinal size, physical size, familiar size, and distance. Rubik's cubes and dice at their typical sizes (5.7 cm and 1.6 cm) and each other's typical sizes were presented during functional magnetic resonance imaging (fMRI) at two distances (25 cm, within reach, vs 91 cm, out of reach). Objects subtended three retinal angles (in degrees): 1.3 for small, far objects; 15.9 for large, near objects; and 4.7 for both small, near and large, far objects. As predicted, univariate contrasts revealed that the dorsal-stream regions - left superior parietal occipital cortex (SPOC) and bilateral anterior intraparietal sulci (aIPS) - activated more for objects in near (vs. far) space, even when retinal angles were matched, and for physically large (vs. small) objects in near space. Higher-order perceptual visual areas - lateral occipital complex (LOC) and the parahippocampal place area (PPA) - distinguished between object identities, showing higher activation for the Rubik's cube (vs. die), consistent with behavioral data showing that even for size- and distance-matched stimuli, the Rubik's cube is perceived as larger (vs. die). Activation in bilateral V1 and PPA increased with retinal size, confirming predicted retinal size coding. Surprisingly, multivariate pattern analysis (MVPA) revealed that, even when the retinal angles are matched, the physical distance of real objects is coded throughout the hierarchy of visual system in both visual streams. Taken together, these results show that real-world distance is a powerful factor that affects activation throughout the visual hierarchy. Although physical distance has been a previously neglected factor in neuroimaging studies of vision, it appears to be a very important one. Distance may be so important because it is essential for determining an object's physical size for both action and recognition and for drawing attention to behaviorally relevant objects in peripersonal space.

Disclosures: M. Maltseva: None. **D.J. Quinlan:** None. **K.M. Stubbs:** None. **T.A. Konkle:** None. **J.C. Culham:** None.

Poster

487. Scenes and Space

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Topic: D.07. Vision

Support: Alfred P. Sloan Foundation FG-2016-6468
Whitehall Foundation 2016-08-18
NIH Grant EY029438

Title: Heterogeneous responses to 3D surface pose in macaque CIP

Authors: *R. DOUDLAH[1], T.-Y. CHANG[1], B. KIM[1], A. SUNKARA[2], A. ROSENBERG[1]; [1]Univ. of Wisconsin-Madison, Madison, WI; [2]Dept. of Surgery, Stanford Univ. Sch. of Med., Stanford, CA

Abstract: A robust three-dimensional (3D) representation of our surroundings, including the pose (orientation and position) of objects, is required to successfully interact with the environment. An unambiguous representation of 3D object pose implies that the shape of 3D orientation tuning curves will be tolerant to the distance at which they are measured. Where and how the visual system achieves a robust 3D visual representation is unclear. Here we evaluate the distance tolerance of 3D orientation tuning in the macaque caudal intraparietal (CIP) area while the monkeys performed an 8-alternative forced choice tilt discrimination task. Planar surfaces were presented at all combinations of tilt (0° to 315° in 45° steps), slant (0° to 60° in 15° steps), and distance (37, 57, 97, and 137 cm). Stimuli were 20° in diameter, defined by random dots (N = 250 dots) with perspective and stereoscopic cues, and presented directly in front of the monkey. We quantified orientation-dependent response modulation at each distance using one-way ANOVAs. Most CIP neurons had significant response modulation at one or more distance (95.3%, 342/359), and 37.3% (134/359) had significant modulation at all four distances, indicating that individual neurons often responded over a broad range of distances. The observed response modulation could reflect selectivity for 3D object pose or local absolute binocular disparities. To dissociate these possibilities, we assessed how much the shape of the orientation tuning curves depended on distance. We defined a distance-orientation tuning invariance (DOTI) index as the mean pairwise correlation between tuning curves measured at different distances with significant modulation. Neurons with disparity selectivity would have low DOTI values, whereas neurons with 3D pose selectivity would have DOTI values closer to 1. A wide range of DOTI values were found (mean = 0.40, SD = 0.28), indicating a continuum of representations ranging from absolute disparity to 3D pose selectivity. High DOTI values were not due to a lack of disparity sensitivity, and therefore indicated tuning for relative disparity gradients. We additionally tested if there is a relationship between CIP activity and the precision of 3D perception by measuring the Fisher Information (FI) carried by each neuron for planar tilt. Across sixteen combinations of slant and distance, the average FI was highly predictive of behavioral sensitivity (Spearman r = 0.96). Together, these results suggest that a more robust 3D visual representation is found in CIP than areas lower in the visual hierarchy, and that the sensitivity of CIP neurons may limit the precision of 3D visual perception.

Disclosures: **R. Doudlah:** None. **T. Chang:** None. **B. Kim:** None. **A. Sunkara:** None. **A. Rosenberg:** None.

Poster

487. Scenes and Space

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Topic: D.07. Vision

Support: Project supported by Shanghai Municipal Science and Technology Major Project Grant No. 2018SHZDZX05

Title: Clustered micro-organization of direction-selective cells in the primary visual cortex of common marmosets

Authors: H.-H. ZENG[1], ***Z.-M. SHEN**[1], M.-M. POO[2];
[1]Inst. of Neuroscience, SIBS, CAS, Shanghai, China; [2]Inst. of Neuroscience, SIBS, CAS, Shanghai City, China

Abstract: Direction-selective cells have been found in the primary visual cortex (V1) of many species. In cats and ferrets, cells with similar preferred directions are spatially clustered. However, in primates, there have been no convincing evidence for columnar organization of directional selectivity. Here, we simultaneously recorded the activity of large neuronal populations of V1 neurons using *in vivo* two-photon calcium imaging and examined the spatial organization of direction-selective cells in marmoset V1. We found that approximately 1/3 of the neurons are direction-selective, and neurons with similar directional preference are highly clustered in both horizontal and vertical directions. Thus, marmoset V1 direction-selective neurons are distributed in a columnar manner. Such micro-architecture is likely to be important for the organization of direction detection of visual signals in the primate brain.

Disclosures: H. Zeng: None. **Z. Shen:** None. **M. Poo:** None.

Poster

487. Scenes and Space

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Support: Alfred P. Sloan Foundation FG-2016-6468
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Title: Heterogeneous responses to 3D surface pose in macaque V3A

Authors: *T.-Y. CHANG[1], R. DOUDLAH[1], B. KIM[1], A. SUNKARA[2], A. ROSENBERG[1]; [1]Univ. of Wisconsin-Madison, Madison, WI; [2]Dept. of Surgery, Stanford Univ. Sch. of Med., Stanford, CA

Abstract: An unambiguous representation of three-dimensional (3D) object pose (orientation and position) is critical for successful interactions with the environment. The neural circuits that create robust 3D visual representations remain unclear. Here we characterized the responses of macaque V3A neurons to 3D surface pose during an 8-alternative forced choice tilt discrimination task. All combinations of tilt (0° to 315° in 45° steps), slant (0° to 60° in 15° steps), and distance (37, 57, 97, and 137 cm) were presented. The stimuli subtended 20° of visual angle, were presented directly in front of the monkey, and were defined by random dot stereograms (N = 250 dots) with perspective and stereoscopic cues. Orientation-dependent response modulation was assessed at each distance using one-way ANOVAs. Most neurons showed significant response modulation at one or more distances (83.5%; 294/352), and 23.3% (82/352) showed significant modulation at all tested distances. Orientation-dependent response modulation could reflect selectivity for 3D pose or local absolute binocular disparities. To dissociate these possibilities, we evaluated if the shape of the orientation tuning curves depended on distance. A distance-orientation tuning invariance (DOTI) index was defined as the mean pairwise correlation between orientation tuning curves with significant modulation at different distances. DOTI values near 1 indicate that the orientating tuning curve shape was invariant to distance (pose tuned). Low DOTI values indicate that the orientation tuning was intolerant to distance (disparity selective). The average DOTI was low (mean = 0.3), indicating that most V3A neurons were not 3D pose tuned. However, the variability in DOTI values was large (SD = 0.31) and some values approached 1, indicating that the orientation tuning of many neurons showed some distance tolerance. This heterogeneity in 3D surface pose responses across neurons suggests a continuum of absolute disparity to 3D pose selectivity. High DOTI values were not due to a lack of disparity sensitivity, indicating that greater pose selectivity reflected tuning for relative disparity gradients. To additionally test for a relationship between V3A activity and 3D perceptual sensitivity, we measured the Fisher Information (FI) carried by each neuron for planar tilt as a function of slant and distance. The average FI of the V3A population was highly predictive of behavioral sensitivity (Spearman r = 0.95). Together, these results suggest that V3A is an intermediate stage in the 2D-to-3D visual transformation, and that the sensitivity of V3A neurons may limit the precision of 3D visual perception.

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Poster

488. Representations of Objects

Location: Hall A

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Program #/Poster #: 488.01/L42

Topic: D.07. Vision

Support: NIH 1R01EY022355

Title: Transformations of object representations across the human visual processing hierarchy

Authors: *V. MOCZ[1], M. VAZIRI PASHKAM[2], M. M. CHUN[1], Y. XU[1];
[1]Psychology, Yale Univ., New Haven, CT; [2]Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Previous work has shown that we can derive transformation functions within lateral occipital cortex (LOC) for affine size and viewpoint changes of objects that may generalize across object categories (Ward et al., 2018, *Journal of Neuroscience*). Additionally, we can derive transformation functions between different brain regions across the visual hierarchy for the spatial response profiles of objects in perception and memory (Favila et al., 2018, *Society for Neuroscience Conference*). In the current study, we explore transformations of object representation, rather than spatial representation, between brain regions. We also explore affine transformations within regions along the ventral and parietal areas of the human visual hierarchy. We used an existing fMRI data set consisting of multiple experiments of human participants (n=6-7 each) performing a 1-back task on images of 10 exemplars of 8 categories (Vaziri-Pashkam and Xu, 2018, *Cerebral Cortex*). We analyzed two experiments, where in one, images were shown in two different sizes, and in the other, images were shown either unaltered or equalized in contrast, luminance, and spatial frequency across all categories. We used linear transformation analysis methods across brain regions of interests (ROIs) along the human visual hierarchy. We then derived transformation functions within an object category that link the pattern of activity between two ROIs and those that link the pattern of activity between two formats of the same category within the same ROI. When mapping from one ROI to another, transformations derived from one object category could significantly predict the representation for new instances of the same object category and all other object categories between V1 and ventral occipitotemporal cortex (VOT), between V1 and superior intra-parietal sulcus (IPS), and between VOT and superior IPS. When linking the affine image transformation of an object category within an ROI, transformations derived from one object category could predict the representation for new instances of the same object category, but this did not generalize to all other object categories. This holds for all the ROIs examined, including V1-V4, VOT, lateral occipitotemporal cortex, and superior IPS. These results suggest that while we may derive category-independent transformations between ROIs across the visual hierarchy, we may only

derive largely category-dependent transformations within an ROI for the two affine image transformations tested here.

Disclosures: **V. Mocz:** None. **M. Vaziri Pashkam:** None. **M.M. Chun:** None. **Y. Xu:** None.

Poster

488. Representations of Objects

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Topic: D.07. Vision

Support: FLAG-ERA JTC 7202070

Title: Modulation of visual responses in mouse superior colliculus in a figure-ground segregation task

Authors: ***J. L. CAZEMIER**, P. R. ROELFSEMA, J. A. HEIMEL;
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Abstract: When using vision to explore the world, a visual scene needs to be segregated into behaviourally relevant blocks: objects. The process of object segregation, despite its complexity, can be performed in a fraction of a second and is seemingly effortless. Previous studies have indicated that neurons in primary visual cortex (V1) show more activity when elicited by figures compared to when elicited by a background. This difference is referred to as figure-ground modulation (FGM). The latency of this modulation suggests that it may be the result of interactions between V1 and higher visual areas. However, recent studies suggest that V1 also influences pop-out effects in superior colliculus, and that superior colliculus can modulate V1 activity via an indirect pathway.
Here, we used multichannel electrophysiological recordings of awake behaving mice to investigate the role of superior colliculus in object segregation. Male C57BL/6J mice were trained to perform a two-alternative forced choice task. In the task, a mouse was shown a figure stimulus embedded in a background that had a different orientation or phase. The mouse would indicate the position of the figure by licking the corresponding side of a lick spout. After training, we recorded electrophysiological signals from superior colliculus during task performance using 16-channel laminar probes.
Multi-unit signals show that both orientation-defined and phase-defined figures elicit FGM in superior colliculus. The onset of FGM is earlier for orientation-defined figures than for phase-defined figures. Further analysis, e.g. comparing FGM onset latency in superior colliculus and V1, investigating the difference in the signal between hits and errors, and analysis of the recorded single units should provide more insight into the role of superior colliculus in object segregation.

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Poster

488. Representations of Objects

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TMDU

Title: Material perception in human and nonhuman primate subjects, compared by the similar discrimination task

Authors: ***M. ITO**, H. TAKEDA, K. FUSHIMI, T. MATSUBARA;
Tokyo Med. and Dent. Univ., Tokyo, Japan

Abstract: Materials on the surface provides a powerful clues to object recognition by perceiving both visual texture information and secondary haptic information, like roughness or hardness. Such material perception is dependent on animal's sensation and experiences. However, the property is not well understood in model animals used for physiological studies. In this study, three monkeys have been trained to perform the material discrimination task, which might be easy for human subjects but very hard for non-human subjects. Then, we examined the relationships between the scores of the material discrimination and the haptic discrimination in both human and non-human subjects for comparison. Thirteen human subjects (6 male and 7 females, age 21-57) conducted two to four daily sessions of the task. In the haptic discrimination task, subjects reported 4 haptic scores (rough/smooth, hard/soft, hot/cold or dry/wet) in 5 steps for each material. In the material discrimination task, subjects reported 5 scores indicating resemblance with 5 reference materials (metal, wood, carpet, gel-sheet, and fur). The task was conducted with or without visual inspection. Order of sample presentation was randomized and each sample was presented once in a daily session. In parallel, three Japanese monkeys (*macaca fuscata*, female, 7.0, 6.8 & 6.9kg) has been trained with the material discrimination paradigm over 35, 29 & 18 months. After pressing a cue-material, they had to touch the same one among 5 reference materials. After the performance has improved above 90%, new object was presented once in a daily session. They have to choose one among 5 reference materials as a response of their categorization. We compared these scores in two dimensional spaces representing haptic and material perception after the modified multi-dimensional scaling procedures. We found that (1) scores of the material and haptic discrimination tended to form compact cluster for each material categories in two dimensional spaces of material and haptic perception, (2) linear regression sufficiently predicted haptic scores from the material scores ($p<0.05$), (3) our material discrimination paradigm was sufficient for direct comparison between human and non-human

primate subjects. In conclusion, material categorization of primate-subjects was largely consistent with human subjects, but showed peculiar differences for some materials, which was dependent on a specific cue-materials as well as a course of training, indicating that they learned properties of materials during the training.

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Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.04/L45

Topic: D.07. Vision

Title: A map of object space in primate inferotemporal cortex

Authors: *P. BAO, L. SHE, M. MCGILL, D. Y. TSAO;
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Abstract: Object recognition lies at the heart of our ability to make sense of the visual world. Befitting the central importance and computational complexity of object recognition, a large piece of brain, inferotemporal (IT) cortex, is dedicated to solving this challenge. However, how the representation of complex visual objects organized in IT cortex is still not clear. Areas selective for a few categories such as faces, bodies, and scenes have been found, but large parts of IT lack any known specialization, leading to uncertainty over whether any general principle governs IT organization. We recorded fMRI and single-unit responses in IT to a large set of objects, and built a low dimensional object space to describe these objects using a deep convolutional network. We found that single IT cells are projecting incoming objects, formatted as vectors in object space, onto specific preferred axes. Remarkably, cells were anatomically clustered into four networks, according to the first two components of their preferred axes, forming a map of object space. Furthermore, this map was repeated across three hierarchical stages of increasing view invariance, and cells comprising these maps collectively harbored sufficient coding capacity to reconstruct arbitrary general objects. These results provide a unified picture of IT organization in which category-selective regions are part of a topographic map.

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Poster

488. Representations of Objects

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NIH/ORIP Grant P51 OD010425

Title: Response dynamics in primate V4 are modulated by perceptual dimensions of visual textures

Authors: *T. KIM, W. BAIR, A. K. PASUPATHY;
Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Past studies have shown that neurons in macaque area V4 play an important role in object recognition by encoding both the geometry of object boundaries and the properties of surfaces, e.g., color, luminance and texture. Recent studies with naturalistic textures suggest that neurons in macaque areas V2 & V4 may process texture information by encoding higher-order image statistics such as the correlations across V1-like filter outputs. Nonetheless, the high dimensionality of such statistics makes interpretation of neural data difficult. Specifically, it is still uncertain how texture encoding in area V4 is associated with human texture perception (e.g., coarseness, regularity, and so on). In this study, our goal was to relate four major dimensions of human texture perception - coarseness, directionality, regularity, and contrast - to the neuronal responses to naturalistic textures. Leveraging methods developed for human psychophysical studies, we first characterized a large database of natural texture images along these four texture dimensions, and then chose a small subset (n = 21) of stimuli that cover a broad range of perceptual qualities of texture. To dissociate the selectivity for a specific orientation (or boundary) within a texture from higher order texture selectivity, each texture image was presented at four orientations (in 45-degree intervals) and at two different sizes (1 x RF, 2 x RF). Overall, we studied the responses of 101 neurons in two awake, fixating monkeys to a set of 168 texture images. We found that approximately 40% of V4 neurons had spiking responses to naturalistic textures that were well explained (i.e., correlation coefficient > 0.5) by a combined selectivity for all four perceptual dimensions. Texture selectivity was highly invariant across different stimulus sizes and orientations. Cluster analyses, used to group texture images based on V4 population activity, resulted in texture groups with clear and interpretable perceptual similarity. Finally, different perceptual dimensions modulated neuronal responses at characteristically different time courses. For example, processing of ‘coarseness’ and/or

‘contrast’ information was significantly faster than that of ‘directionality’ and ‘regularity’. These results indicate that texture selective V4 neurons encode key psychophysical measures of texture by computing simple summary statistics with different temporal dynamics.

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Poster

488. Representations of Objects

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Topic: D.07. Vision

Support: NIH Grant EY029420

Title: Solid shape representation in biological and artificial vision

Authors: *R. SRINATH[1,2], Q. A. WANG[1,2], K. J. NIELSEN[1,2], C. E. CONNOR[1,2];
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Abstract: Vision requires transforming 2D images into knowledge about 3D physical reality. Here, we found that this transformation occurs explicitly in surprisingly early stages of both biological vision (in area V4 of the primate ventral pathway) and artificial vision (convolutional layer 3 of AlexNet, an established model for area V4).
To study the representation of solid versus planar shape, we recorded from single V4 neurons, using the responses to initially random shapes to guide the evolution of subsequent stimulus generations. By comparing responses between shaded solid shapes and planar silhouettes with identical boundaries, we found that a majority of V4 neurons are selectively tuned for solid shape as opposed to planar shape. Solid shape responses were consistent across a variety of 3D shape cues including reflective and refractive material, glossy and matte shading, and binocular disparity. Response-weighted averaging (RWA) analysis in 3D geometric space revealed that V4 neurons are tuned for 3D solid shape fragments defined by the surface and medial axis geometry of shafts, junctions, and terminations. Thus, the ventral pathway quickly shifts from image signals to representations of solid, 3D shape elements.
To investigate whether deep convolutional networks also process 3D shape in intermediate layers, we quantified shape responses of single nodes in the convolutional and fully-connected layers of AlexNet. We used the same stimuli evolved during the neurophysiological experiments and extracted activations of single nodes in AlexNet. For each V4 neuron, we searched for the node in convolutional layer 3 with the most highly correlated responses. We found surprisingly high correlations, with a median of 0.47, and 25% of correlations above 0.55. Strikingly, the 3D selectivity of these nodes was highly correlated with the 3D selectivity of the corresponding V4 neurons (correlation coefficient of 0.64). We also performed the same evolving stimulus

experiment on convolutional layer 3 nodes, characterized their shape tuning with RWA matrices, and observed tuning for 3D shape fragments similar to V4 neurons.
Our results suggest that artificial vision networks succeed in part by implementing an internal representation of 3D physical reality, even though the inputs are 2D images and the outputs are signals for semantic object categories, and thus 3D representations are not externally imposed in any way. In spite of their differences, biological and artificial vision networks find a similar solution, evolving internal representations of the 3D physical elements that make up the real world they interact with.

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Poster

488. Representations of Objects

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Title: Short-term memory for border ownership in cortical area V4

Authors: *T. P. FRANKEN, J. H. REYNOLDS;
SNL-R, The Salk Inst. for Biol. Studies, La Jolla, CA

Abstract: A key step in understanding a visual scene is to identify the borders that separate figure from ground and to assign ownership of each border to its figure. Pioneering work conducted by Rudiger von der Heydt and colleagues identified neurons in early visual cortex (mainly in area V2) that respond according to which side of a border belongs to a figure (border ownership sensitive neurons), even if the stimulus information that differentiates figure from ground falls outside of the neuron's classical receptive field (Zhou et al., 2000). Such neurons can display short-term memory for border ownership (O'Herron and von der Heydt, 2009). It has been proposed that neurons in downstream areas may provide feedback signals that help establish border ownership sensitivity in early visual cortex. If this hypothesis is correct, similar short-term memory is expected to be present in these downstream areas. To explore this possibility, we studied the physiology of border ownership in area V4, a major source of feedback to V2. We recorded single- and multi-unit activity in V4 of the awake macaque. We used a pseudorandom sequence of patches with square-wave gratings (8 colors, 6 orientations) to

map each unit's receptive field. We then presented a luminance and color-defined object (square) at different locations on a plain background. To match sensory conditions across figure and ground, the color and luminance of the square and background were reversed on half of all trials. To test for short-term memory for border ownership, we then, after showing figure and ground, removed all stimulus cues to border ownership. We analyzed neuronal responses for object locations for which one of the square's borders overlapped with the receptive field. By comparing spike rates across trials on which the position of that border was identical for different object locations (on opposite sides of the border), we could determine border ownership sensitivity. As has been reported by Zhou et al. (2000), we find that a substantial fraction of V4 units are sensitive to border ownership. In addition, we find that many of these units show persistent border ownership signals after the display was rendered ambiguous. Our findings show that short-term memory for border ownership is not limited to early visual cortex but is also strongly present in V4.

Disclosures: T.P. Franken: None. **J.H. Reynolds:** None.

Poster

488. Representations of Objects

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Topic: D.07. Vision

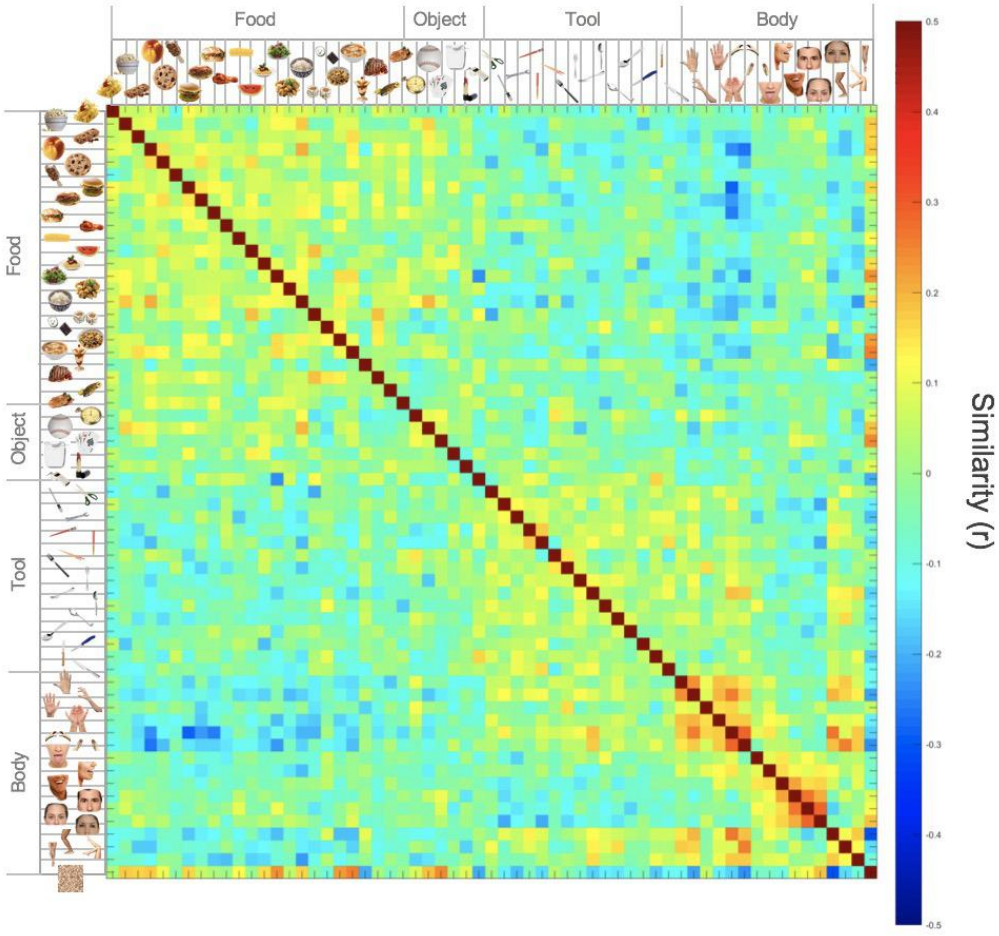
Support: Canada First Research Excellence Fund "BrainsCAN" grant to Western University
Natural Sciences and Engineering Research Council of Canada

Title: Decoding representations of food images within the ventral visual stream

Authors: *C. CORICELLI[1], K. M. STUBBS[2], R. I. RUMIATI[1,3], J. C. CULHAM[2]; [1]Cognitive Neurosci., Intl. Sch. For Advanced Studies (SISSA), Trieste, Italy; [2]Brain and Mind Institute, Univ. of Western Ontario, London, ON, Canada; [3]ANVUR, Rome, Italy

Abstract: Neuroimaging studies have revealed food-selective activation across a broad network of human brain regions, including areas within the ventral visual stream implicated in visual object recognition. However, the nature of visual food representations is unknown. Moreover, we eat by using hands and utensils to bring food to the mouth, perhaps invoking associations with hand, tool- and mouth-selective regions of the lateral occipitotemporal cortex (LOTC). We used representational similarity analysis (RSA) on data from functional magnetic resonance imaging (fMRI at 3 Tesla) in a selected region of interest (ROI) in left LOTC to investigate whether visual representations of food stimuli are distinct from other visual categories (i.e. other objects). To this end, healthy normal-weight individuals (n=22) performed a one-back task in the scanner

while viewing colored pictures of different object categories (food, body parts, utensils, objects, scrambled food images), matched for retinal size. Consistent with previous literature, univariate contrasts of activation levels (random-effects general linear model; false discovery rate corrected with $p < .01$) revealed food-selective activation (food > other stimuli) within a network of regions, including insula, fusiform gyrus, amygdala, putamen and orbito-frontal cortex. Nevertheless, RSA revealed distinct activation patterns for food stimuli. That is, food representations in left LOTC were highly correlated within-category but distinct from the representations for food-associated items (i.e. tools, hands and mouths, Figure 1). No strong evidence that food representations are more similar to food-associated items compared to unrelated items (i.e. legs) in left LOTC was found. Taken together, these results suggest that although food images evoke activation that overlaps with other visual categories, the neural representation of food is distinct.



Disclosures: **C. Coricelli:** None. **K.M. Stubbs:** None. **R.I. Rumiati:** None. **J.C. Culham:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.09/M4

Topic: D.07. Vision

Support: grant 2013070 from the US-Israel Binational Science Foundation (LYD and RTK)
NINDS R37NS21135 (RTK)

Title: Distributed representation of temporally persistent visual categories

Authors: *L. Y. DEOUELL[1], G. VISHNE[2], E. M. GERBER[3], R. T. KNIGHT[4];
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Abstract: Research on visual perception has thoroughly characterized the neural activity in response to the appearance of visual stimuli. These responses often reflect the category of the stimuli, but they are transient. In reality, our visual experience is composed of many moments without change, where we still maintain information about our surroundings, yet these periods of sustained viewing have been mostly neglected by past research. We set out to fill this gap and characterize neural tracking of category information beyond the initial moment of change. This was done using intracranial recordings from 10 subjects undergoing surgery for intractable epilepsy (1067 electrodes). Patients viewed images of variable durations (300-1500ms) from several categories, coupled with an identification task to maintain attention. Previously (Gerber et al., 2017), we identified the single electrode correlates of persistent categorical information and found only two electrodes in the posterior fusiform face-selective region that were sensitive to category membership until the end of the stimulus duration. Here, we move to characterize the dynamics of ongoing category selectivity using multi-variate pattern analyses. We trained a classifier (linear discriminant analysis) to distinguish between viewing of objects and faces on a moment by moment basis. Additionally, we used the temporal generalization method (King & Dehaene, 2014), training and testing the classifier on different time-points in order to identify changes in the multi-site pattern. The classification was based on broadband high frequency activity (>30Hz) which was shown to correlate with local neural firing. Sustained selectivity for category information was measured by classifying stimuli of duration ≥900ms. We found sustained categorical selectivity in two subjects. Classifier performance was above chance until the end of the stimuli duration, well after the onset response for category selectivity. Using the temporal generalization method, we show that the pattern of category selectivity remained similar throughout the duration of the stimulus. In both subjects there was a single electrode showing sustained category sensitivity, but importantly, reduced sets of electrodes excluding this

electrode also showed the same pattern of sustained categorical response, meaning that category information might be maintained by more extended regions, even when local categorical information cannot be detected.

Disclosures: L.Y. Deouell: None. **G. Vishne:** None. **E.M. Gerber:** None. **R.T. Knight:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.10/M5

Topic: D.07. Vision

Support: NDSEG Fellowship
NIH Grant EY014681
RII Track-2 FEC: Neural Basis of Attention

Title: Processing of movement-shape associations in inferior temporal cortex

Authors: *D. BURK, D. L. SHEINBERG;
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Abstract: As we move throughout the world, our brains continuously acquire sensory information and make predictions when visual information is limited. For example, an animal hopping in a foggy park could be perceived as a rabbit or a frog, even when the animal's shape is obscured. How does the hopping movement lead to potential animal identity? More generally, objects often have stereotypical movements, but it remains unknown how movement is used in object recognition. Previous research has shown that the brain associates features (e.g. color, shape, size) to create a unified percept of an object. It remains unknown how visual areas traditionally recognized for processing certain object features, integrate or bind secondary features. Little is known about how motion might affect responses in inferior temporal cortex (area IT) during object recognition. Here we ask whether motion can drive responses in inferior temporal cortex during a task that requires selection of shapes based on motion information. To investigate this, we developed a match-to-sample task for non-human primates that requires subjects to identify moving shapes with variable perceptual noise. Subjects are trained to associate two categories of shapes with category specific motion paths. Behavioral data demonstrates that motion or shape information is used depending on the availability of shape information. We used a pattern classifier to decode motion information from a population of IT neurons recorded during the task and a passive viewing variant. Preliminary data from one animal shows that while motion does not drive IT neurons in the absence of shape information, motion can modulate responses and lead to changes in selectivity. Furthermore, preliminary data suggests that inferior temporal cortex has access to motion information during the active task

where pursuit was allowed, as well as passive viewing where fixation was required. Linear regression analysis showed that local position differences alone could not account for differences in neuronal responses in the active task. Here we aim to demonstrate that learning of associations between movements and shapes can lead to changes in responses in inferior temporal cortex. These findings support a role for integration of motion and shape information in a traditional "shape-processing" area, inferior temporal cortex.

Disclosures: D. Burk: None. **D.L. Sheinberg:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.11/M6

Topic: D.07. Vision

Support: CIHR grant 366062).

Title: Pattern separation in ventral visual stream

Authors: *K. M. FERKO[1], A. BLUMENTHAL[3], D. PROKLOVA[5], C. B. MARTIN[4], T. BUSSEY[6], L. M. SAKSIDA[1], A. KHAN[2], S. KOHLER[7];
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Abstract: Pattern separation is a neural computation thought to underlie our ability to form distinct memories of similar events. It involves transforming overlapping inputs into less overlapping outputs. Research on pattern separation has primarily focused on transformations of representations between entorhinal cortex and the dentate gyros of the hippocampus in the context of memory tasks. Pattern separation may, however, also occur in other cortical regions and may not be limited to computations that support memory processing. In the ventral visual stream (VVS) there is considerable evidence for hierarchicaltransformation from feature-based visual representations to conjunctive whole-object representations, with the latter allowing for distinct coding even when objects have significant feature overlap. In the current study, we asked whether this transformation can be understood as pattern separation, and whether pattern separation can be observed even outside the context of classic recognition-memory tasks. To investigate pattern separation in the VVS, we combined fMRI in humans (N=23) with multivariate pattern analyses techniques and compared representations of visual objects in a mid-level visual region, Lateral Occipital Complex (LOC), with those in the region proposed to be at the top of the VVS object processing hierarchy, Perirhinal Cortex (PrC). We presented images of

objects from multiple categories, with differing degrees of visual similarity among exemplars. We administered a variant of a 1-back task with catch trials that required identification of repetition either at the exemplar or category level. For analyses, we grouped exemplars within each category into three levels of perceived visual similarity (low-medium-high) based on participants' own ratings. Behavioural results indicate sensitivity of performance to these varying levels of similarity. Imaging results obtained using Support Vector Machine classification revealed differences in pattern similarity between representations of exemplars in LOC and PrC. Specifically, while patterns in LOC could be distinguished successfully only at the lowest level of visual similarity within categories, patterns in PrC could be distinguished at all levels of similarity. Because patterns at higher levels of visual similarity are overlapping in LOC, but can be differentiated in PrC, these results provide evidence for pattern separation in the VVS.

Disclosures: K.M. Ferko: None. **A. Blumenthal:** None. **D. Proklova:** None. **C.B. Martin:** None. **T. Bussey:** None. **L.M. Saksida:** None. **A. Khan:** None. **S. Kohler:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.12/M7

Topic: D.07. Vision

Title: Activation of high-level visual object representations by spatial frequency magnitude

Authors: *M. ØVERVOLL;
Dept. of Psychology, Uit - The Arctic Univ. of Tromso, Tromso, Norway

Abstract: Structural information is considered to be central for object identification. However, a neural code based on spatial frequency magnitude without structural information may play an independent functional role, for example by supporting efficient within and between category comparisons, and could be sufficient for activating high-level visual object representations. To investigate this possibility, grayscale images of typically red and green objects (e.g., strawberry, broccoli) were phase scrambled, and the resulting images were colored (red or green: congruent/incongruent). Phase scrambling randomizes the structural information in an image while preserving the spatial frequency magnitude. Thus, if spatial frequency magnitude can activate high-level object representations, there should be enhanced processing of phase-scrambled images with congruent colors, as high-level representations can modulate the processing of low-level features, causing stronger responses to features that are typically associated with the object category. In each trial, the stimulus was presented for 1 sec before the color began flickering off/on at a rate of 10 Hz. After 2.5 sec, a circular patch with the same color as the image appeared gradually (opacity 0-100%), with opposite phase, at a random location in the image until response was given or 5 sec had passed. The participants' task was to

press the response key when the color patch was detected. EEG was recorded from 32 locations based on the 10-20 system. Following ocular artifact removal, surface Laplacian was applied to the EEG data using the Perrin algorithm. Occipital (Oz) phase-locked power and inter-trial phase coherence were higher for congruent than incongruent stimuli, and detection threshold was lower for congruent than incongruent stimuli. An analysis of connectivity degree (10 Hz) during the flicker period for both conditions revealed high overall connectivity for prefrontal (Fp1/Fp2) and temporoparietal (P7/P8) regions. Further connectivity analyses (weighted phase lag index) for these regions revealed greater synchronization between Fp1/Fp2 and Oz for congruent stimuli than for incongruent stimuli, indicating enhanced prefrontal-occipital feature maintenance for colors that are associated with the object category. The results suggest that high-level visual object representations can be activated by spatial frequency magnitude, independent of structural information.

Disclosures: M. Øvervoll: None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.13/M8

Topic: D.07. Vision

Support: NIH EY022671

Title: Core visual object recognition behavior in common marmosets

Authors: S. L. BOKOR, A. J. E. KELL, Y. JEON, T. TOOSI, *E. B. ISSA;
Neurosci., Columbia Univ., New York, NY

Abstract: Humans and macaques can recognize visual objects in natural scenes at a glance, despite identity-preserving transformations in the view, size, and position of an object. This ability, known as core visual object recognition, reflects a remarkable computational feat that only recently was accomplished at human levels by computer vision systems such as artificial neural networks. Here, we quantify the core object recognition abilities of the common marmoset, among the smallest of the anthropoid primates (monkeys, apes, and humans). Critically, as an anthropoid primate, the marmoset is endowed with a high-acuity fovea at its visual input and an elaborated set of ~150 cortical areas, unlike other small mammalian models such as rodents and tree shrews. It remains unclear, however, whether this small monkey performs invariant object recognition at levels comparable to and with similar behavioral signatures (e.g., image-by-image performance patterns) as larger monkey models in neuroscience such as macaques. To test marmoset visual behavior, we adopted a variant of an operant-conditioned object recognition task previously used in macaques and developed a novel

homecage system for high-throughput behavioral testing in marmosets. We computationally benchmarked our task on a commonly used deep neural network (Alexnet) to assess the difficulty of the visual discrimination component in a visual system without downstream noise or behavioral lapse. The two-object visual discrimination proved computationally challenging: early layers of Alexnet perform near chance levels (50%) whereas higher layers achieve ~80% performance. Our preliminary findings demonstrate that marmosets: (1) complete 500-1500 trials per day (in a 3-hour period); (2) reach performance levels of ~90% on the relatively simple task of pose-tolerant object recognition on blank, gray backgrounds, suggesting low behavioral lapse rates; (3) reach performance levels of >80% on the visually difficult core object recognition task on complex natural backgrounds that was benchmarked on Alexnet; (4) exhibit behavioral signatures (image-by-image performance) that are highly correlated with those of macaques. Taken together, these findings suggest that marmosets and macaques may exhibit similar visual behavior, complementing known similarities at the level of the eye and brain across anthropoid primates. Thus, marmosets may be a valuable, small animal model for neuroscientific studies of high-level visual object recognition.

Disclosures: **S.L. Bokor:** None. **A.J.E. Kell:** None. **Y. Jeon:** None. **T. Toosi:** None. **E.B. Issa:** None.

Poster

488. Representations of Objects

Location: Hall A

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Program #/Poster #: 488.14/M9

Topic: D.07. Vision

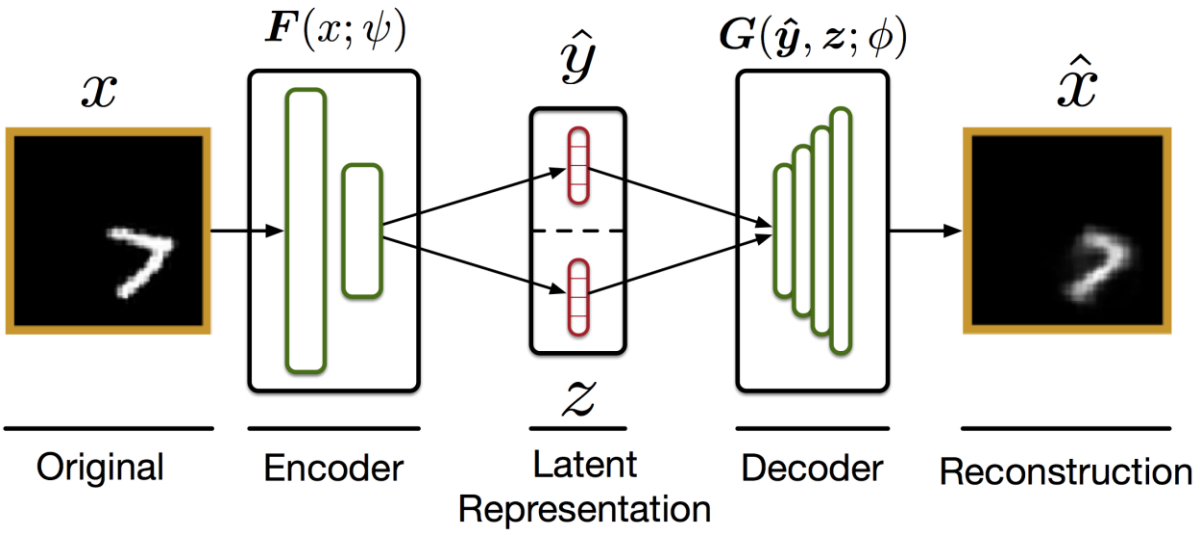
Support: Department of Defense (DoD) through the National Defense Science & Engineering Graduate Fellowship (NDSEG) Program

Title: Disentangling “what” and “where” visual information in neural network vision models

Authors: *E. CHRISTENSEN[1], J. ZYLBERBERG[2];
[1]Physiol. and Biophysics, Univ. of Colorado, Aurora, CO; [2]Physiol. and Biophysics, Univ. of Colorado Sch. of Med., Aurora, CO

Abstract: Across a variety of species, the "two-stream" organizational structure of cortical visual processing is highly conserved. A single input source (LGN) is eventually de-mixed into the dorsal (‘where’) stream and the ventral (‘what’) stream. The ‘what’ and ‘where’ in the input space (pixel space) is entangled and represented by an overlapping subset of pixels and must be disentangled to extract this information. How do networks of neurons in the brain disentangle this information from a common source? Where along this pathway is the entangled information split into two outputs? Recent advances in computer vision facilitate answering questions like

these. Training models to concurrently decompose a scene into a multi-faceted representation may confer a generalization advantage. I hypothesize computer vision models that disentangle object identity and location information from scene images will learn more robust visual representations. Vision models that extract multi-faceted information from images will enable more sophisticated and robust autonomous agents capable of visually navigating complex environments the way primates can. Using artificial neural networks (ANN) as a model of visual cortex I trained a simplified vision model to recognize objects while retaining sufficient information to reconstruct the scene. This model is comprised of an encoder, which learns a compressed representation of an image scene and a generator, which attempts to reconstruct the image scene from the representation. Models trained to reconstruct images displayed better generalization and categorization accuracy even when trained with on increasingly unreliable or corrupt data (random labeling of fractions of the data). After training, I examined Shannon mutual information of the output units in the hidden representation. Several model neurons in the scene representation spontaneously learn independent representations of an objects location in the image.



Disclosures: **E. Christensen:** None. **J. Zylberberg:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.15/M10

Topic: D.07. Vision

Support: Simons foundation
NIH

HHMI

Title: Neural code of face memory in the macaque IT and perirhinal face patches

Authors: *L. SHE[1], M. K. BENNA[2], S. FUSI[2], D. Y. TSAO[1];
[1]Caltech, Pasadena, CA; [2]Neurosci., Columbia Univ., New York, NY

Abstract: The role of face-selective regions ("face patches") in inferior temporal (IT) cortex in face memory remains unclear: how is a new face remembered, and how is this memory re-activated during perception? To address this, we recorded single neurons from two face patches, face patch PR in perirhinal cortex, a region that has been strongly implicated in processes related to visual memory, and face patch AM in anterior IT cortex. We found that PR contains a high concentration of face-selective cells. In both PR and AM, cells are modulated by both face identity and familiarity, and exhibit stronger, prolonged responses to unfamiliar compared to familiar stimuli. Further measurement of neuronal responses to thousands of parametrized unfamiliar faces revealed that for representing unfamiliar faces, a substantial population of PR cells inherit the "axis code" previously found in IT face patches (Chang and Tsao, Cell 2017), which is a low dimensional, linear representation of unfamiliar stimuli. However, for representing familiar faces, PR uses a different code, weakly related to that for unfamiliar faces. A similar deviation from the axis code for familiar faces was observed in AM. Finally, we found a small number of very sparse, 'grandmother cell'-like cells in PR, responding only to a single or a few faces, often personally familiar. These cells might contribute to the memory storage of individual instances of faces. Together these results suggest that PR cells implement a critical stage in face memory storage and retrieval, and may facilitate association between semantic and perceptual memories.

Disclosures: L. She: None. **M.K. Benna:** None. **S. Fusi:** None. **D.Y. Tsao:** None.

Poster

488. Representations of Objects

Location: Hall A

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Program #/Poster #: 488.16/M11

Topic: D.07. Vision

Support: HHMI
Swartz Foundation

Title: Understanding the brain's code for 3D objects via immersive virtual reality

Authors: *E. KOCH, B. HAGHI, D. Y. TSAO;
Caltech, Pasadena, CA

Abstract: Primate interaction with objects and agents in the visual world requires the brain to construct a 3D model of the environment and the objects within it. For example, even the simple action of grabbing a stick off the cluttered forest floor requires localizing the stick within the scene and with respect to self, and building an internal model of the shape and pose of the stick. Localization of the brain's core geometric engine, and the rules by which the neurons working as part of this module to parse and encode 3D scenes remains unknown. The advances and commercialization of virtual reality headsets provide an exciting tool for probing the brain's code of 3D object representation via immersion into realistic 3D environments, while still preserving the experimental ability to systematically change scene parameters. We have made modifications to the hardware and software of a virtual reality headset with built-in eye tracking (FOVE Inc.) to match a macaque's inter-ocular distance and smaller head. One candidate for the brain's geometric engine is area CIPS (Caudal Intraparietal Sulcus). We localized area CIPS by comparing fMRI activation to disparity-rich stimuli (rippled planes, 3D objects, buildings, and disjoint planes) versus zero disparity stimuli (flat planes) (Tsao et al., 2003). We then targeted CIPS for physiological recordings while immersing the monkeys in a variety of rendered 3D scenes via the modified headset. We tested each CIPS neuron on a large number of 3D stimuli, including flat and curved objects of different sizes, 3D positions, and shapes, to characterize the selectivity of these neurons to a range of geometric parameters. We also analyzed selectivity of units in machine learning algorithms trained on 3D scene reconstruction, and compared the 3D representations in these networks to that in CIPS.

Disclosures: E. Koch: None. **B. Haghi:** None. **D.Y. Tsao:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.17/M12

Topic: D.07. Vision

Support: HHMI
HFSP
Simons Foundation

Title: Neural correlates of perceptual switches in binocular rivalry without active report

Authors: *J. K. HESSE[1], V. WADIA[1], U. RUTISHAUSER[2], D. Y. TSAO[1];
[1]Caltech, Pasadena, CA; [2]Dept. of Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: When two incongruent stimuli are presented to the two eyes, the conscious percept alternates between them, even though the physical input stays constant. This paradigm, also known as binocular rivalry, offers an entry point to study how switches between conscious

interpretations of ambiguous stimuli are represented and broadcasted across the brain. Logothetis et al. (e.g. 1996) measured across different brain regions the extent to which neural activity was modulated by reported switching. However, Fraessle et al. (2014) reported that during active report, modulation by conscious percept is confounded with the act of reporting itself, and that when active report is stopped, modulation vanishes in most parts of the human brain.
We thus set out to study which brain regions show switching behavior during binocular rivalry similar to that during physical switches, and whether this switching requires active report. We performed both single electrode and multi-electrode population recordings in monkeys and humans from a number of areas including amygdala, SMA, and face patches in inferotemporal and prefrontal cortex, while reading out the conscious percept using a novel no-report paradigm. In humans, we also contrasted modulations with active report. Our results allow us to disentangle which neural signatures represent switches of the conscious percept rather than the mere report of it.

Disclosures: J.K. Hesse: None. **V. Wadia:** None. **U. Rutishauser:** None. **D.Y. Tsao:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.18/M13

Topic: D.07. Vision

Support: HHMI

Title: Probing the neural substrates of visual imagination in humans

Authors: *V. WADIA[1], J. K. HESSE[1], A. MAMELAK[2], U. RUTISHAUSER[2], D. Y. TSAO[1]; [1]Caltech, Pasadena, CA; [2]Dept. of Neurosurg., Cedars-Sinai Med. Ctr., Los Angeles, CA

Abstract: Intelligent beings are able to form a coherent model of the world, one that is developed through an active interaction with our environment. The existence of this internal model has several consequences including generating context-appropriate behavior flexibly, efficient planning and one shot learning. It also contributes to the greatly enhanced visual inference capabilities we enjoy relative to machines. Mammalian visual processing has long been thought of as a combination of top down and bottom up processing. An extreme instance of top-down processing occurs in imagination, when a subject can be directed by verbal cues to perceive a stimulus in the absence of any bottom-up input. Animal studies have yielded rich insight into neural mechanisms for bottom-up processing. However, the neural mechanisms for top-down processing have been more elusive, in part due to the impossibility of verbal instruction in animals. Here, we examine the neural mechanisms underlying visual imagination in humans. We performed single-neuron recordings in the medial temporal lobe of epilepsy

patients implanted with depth electrodes with embedded microwires for the purpose of localizing the source of their focal epilepsy. We first map the feature selectivity space of the recorded visually selective cells to a large set of object stimuli and then compare responses of the same cells during a passively viewed vs. imagined setting.

Disclosures: V. Wadia: None. **J.K. Hesse:** None. **A. Mamelak:** None. **U. Rutishauser:** None. **D.Y. Tsao:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.19/M14

Topic: D.07. Vision

Support: HHMI

Title: The code for occluded faces in IT cortex

Authors: *Y. SHI, D. Y. TSAO;
Caltech, Pasadena, CA

Abstract: Inferior temporal (IT) cortex is considered the final stage for object recognition in the ventral visual stream. While much progress has been made in IT to understand the code for intact objects, objects in the wild are mostly occluded. How do we recognize occluded objects as easily despite a broad range of information loss? How are occluded objects represented in IT cortex? To address these questions, we performed extracellular recordings in face patch ML of macaque IT cortex. During recording sessions, monkeys passively viewed 13 occluded face sets. Every face set was made from the same 20 intact faces by adding different occlusions. Single-cell responses to occluded faces change dramatically from those to intact faces, both in amplitude and dynamics. Cells showed consistent tuning to occlusion types for every face identity but not vice versa. As a whole, the face cell population encoded different occlusion configurations as separate clusters in the neural space. The distance between representations of occluded and intact faces in the neural space was strongly affected by the side and area of the occluders as well as the information density beneath the occluders. Together, these results argue against amodal completion of occluded face components prior to the middle face patch, and raise the question, how is the brain able to determine facial identity of occluded faces despite such drastic changes in neural responses to occluded compared to intact faces?

Disclosures: Y. Shi: None. **D.Y. Tsao:** None.

Poster

488. Representations of Objects

Location: Hall A

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Program #/Poster #: 488.20/M15

Topic: D.07. Vision

Support: HHMI
NIH Grant DP1-NS083063

Title: Behavioral tools for studying object vision in the northern tree shrew

Authors: *F. LANFRANCHI[1], J. B. WEKSELBLATT[2], F. LUONGO[3], D. Y. TSAO[4];
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[4]Caltech, Pasadena, CA

Abstract: The macaque monkey has classically provided a key model for visual processing, due to its amenability to psychophysical tasks and well-delineated visual hierarchy. More recently, the rodent has emerged as a new model for visual processing, due to the availability of molecular and genetic tools. An ideal model system would satisfy both needs: amenability to complex psychophysical tasks and tractablility for molecularly-based recording and perturbation techniques. Towards this goal, we have embarked on an effort to establish the northern tree shrew as a model organism for study of high-level object vision.
A diurnal animal, the tree shrew has high visual acuity (>10x that of rodents), a cone-dominant retina, and a columnarly-organized visual cortex. Moreover, tree shrew cortex is lissencephalic, enabling increased optical access for imaging neural circuit dynamics compared to the macaque. Due to its small size (~150-200 grams) and relatively short reproductive and developmental cycles (6 weeks gestation, 4-6 months from birth to adulthood, 1-6 offspring per litter), the tree shrew offers experimental and genetic accessibility similar to rodents. We have built a high-throughput, low-cost, automated behavioral apparatus allowing visual behaviors in the tree shrew to be rapidly assayed. We report our initial results training tree shrews on figure-ground and object discrimination tasks. The animals readily learned to self-initiate trials and performed upwards of 1000 trials per day. Initial comparisons demonstrate that tree shrews learned significantly faster than mice or rats on the same tasks. Future work will incorporate head-fixed paradigms, electrophysiological, and optical recordings of neural activity during these tasks.
This work is supported by HHMI and DP1-NS083063.

Disclosures: F. Lanfranchi: None. **J.B. Wekselblatt:** None. **F. Luongo:** None. **D.Y. Tsao:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.21/M16

Topic: D.07. Vision

Support: KAKENHI 15H05919

Title: Spatial and time-frequency representations of glossy material properties in the monkey inferior temporal cortex

Authors: *K. KAWASAKI[1], H. MIKI[2], K. ANZAI[2], M. SAWAYAMA[3], T. MATSUO[4], T. SUZUKI[5], I. HASEGAWA[1], T. OKATANI[6];
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Abstract: An object can be ideally created from arbitrary materials. A cup can be made of plastic, glass or ice. By means of material or shitsukan perception we can settle to an appropriate choice. It has been shown that the inferior temporal cortex (ITC) plays a pivotal role in both object and material perception. Previous neurophysiological studies about material perception mainly focused on gloss processing in view of the distribution of specular reflection and suggest that gloss strength and sharpnessare encoded by a subpopulation of IT neurons. Gloss is however modulated not only by specular reflection but also by other object properties including the material of which the object is made. To comprehensively understand the role of ITC for material perception, in the present study we conducted the electrocorticography (ECoG) recording from ITC while the monkey engaged in a passive visual fixation task presenting the object images with multidimensional material properties. We specifically rendered three-dimensional computer graphics objects with manipulating five material dimensions of gloss strength, gloss sharpness, translucency, change from metal to glass (metal/glass), change from metal to plastic (metal/plastic). A 128-channel ECoG electrode was placed covering whole ITC area including the lower bank of the superior temporal sulcus. Visual evoked response was recorded and event related spectral perturbation was calculated. The response selectivity in six frequency bands, delta, theta, alpha, beta, low-gamma and high-gamma along the five dimensions was examined. The selectivity for gloss strength was appeared in all frequency bands. Selective electrodes was observed pronouncedly in the anterior part of the ITC for delta, theta, beta and high gamma bands. Selectivity for gloss sharpness was prominent along the whole ITC for beta and low-gamma bands and the middle and the anterior parts of the ITC for

alpha band. Response selectivities for translucency, metal/glass and metal/plastic dimensions were commonly prominent in the posterior part of the ITC but in frequency domain, the metal/ glass and the other two dimensions were separable. Selectivity for the metal/ glass dimension was pronounced only for alpha band, but for the other two dimensions selectivities were pronounced for delta, theta, alpha and low-gamma bands. These results indicate that multiple material properties are represented in the overlapped specific spatial-frequency domains in ITC.

Disclosures: K. Kawasaki: None. **H. Miki:** None. **K. Anzai:** None. **M. Sawayama:** None. **T. Matsuo:** None. **T. Suzuki:** None. **I. Hasegawa:** None. **T. Okatani:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.22/M17

Topic: D.07. Vision

Support: NSF 81430010
NSF 31627802
China Ministry Sci Tech 2015AA020515

Title: Curvature domains in V4 of macaque monkey

Authors: *J. HU, X. SONG, A. W. ROE;
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Abstract: Previous studies have shown that neurons in V4 are involved in shape encoding, and that some neurons prefer highly curved shape while other neurons prefer straight contours (Carlson et al Curr Biol 2011; Nandy et al., Neuron 2013, 2016). Here, we hypothesize that neurons that prefer curves tend to cluster and to form functional domains, distinguishable from 'orientation domains' which exhibit preference for straight lines. Using intrinsic optical imaging, we imaged V4 in anesthetized macaque monkeys using moving curved gratings at 4 orientations (up, down, left, right), and straight and curved flashing single lines. These maps were compared to maps obtained in response to orientation (standard 'straight contour' moving gratings at 0°, 45°, 90°, 135° orientations), isoluminant color vs achromatic gratings, and high vs low spatial frequency gratings. By statistically comparing and contrasting the different types of maps, we found the presence of domains more responsive to curved than to straight gratings. These domains exhibited significantly stronger response to curvature of a single preferred orientation than to the same curvature at different orientations or to straight lines. As assessed by cross correlation, maps to curvature stimuli of similar orientation were more similar than when compared to those of different orientation or to straight gratings. Spatially, the distribution of these domains were distinct from orientation domains, color preference domains, and high spatial

frequency preference domains. These domains exhibited a degree of spatial invariance consistent with reports from single unit studies.Our data show that there are ‘curvature’ domains within V4 that exhibit preference for curved over straight contour stimuli with preference for a particular curvature orientation. Moreover, these regions form a unique spatial distribution pattern distinguishable from standard functional maps including maps for orientation, color, and spatial frequency. These results are consistent with and extend previous single unit studies of V4. We suggest that, similar to V1 and V2, components of object shape encoding exist in functional domains of V4.

Disclosures: J. Hu: None. **X. Song:** None. **A.W. Roe:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.23/M18

Topic: D.07. Vision

Title: Investigating ventral stream computations in the mesopallium and entopallium of the pigeon brain

Authors: *W. J. CLARK, B. S. PORTER, M. COLOMBO;
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Abstract: The mammalian ventral visual stream exhibits a progressive increase in the complexity of receptive field preferences for categories of visual stimuli along a posterior-anterior axis in primate extrastriate visual cortex, reflecting these neuron’s function in complex pattern recognition. The avian visual nuclei exhibit a feed-forward increase in the complexity of receptive field preferences that recent electrophysiological investigation suggests may emerge with categorical representation of object categories in the anterior mesopallium of the dorsal ventricular ridge (DVR). We performed electrophysiological recordings along a reciprocal pathway between the anterior entopallium and mesopallium in four pigeons while they performed a passive fixation task during which they viewed images belonging to five object categories (human faces, pigeon faces, scrambled face controls, and sine wave gratings). A population of visually responsive neurons in the mesopallium exhibited category-selective responses, with a sub-category firing selectively only to images of pigeon and human faces. The complex preferences of visual neurons in the anterior mesopallium suggests that the avian visual system may recapitulate information using similar mechanisms to those in the primate ventral visual stream. These observations lend support to the view that birds encode sensory representations in parallel processing streams that are homologous with neocortical columns, despite the fact birds group functionally similar cell-classes into dense nuclear clusters that are interconnected, but spatially dispersed in the DVR.

Disclosures: **W.J. Clark:** None. **B.S. Porter:** None. **M. Colombo:** None.

Poster

488. Representations of Objects

Location: Hall A

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Program #/Poster #: 488.24/M19

Topic: D.07. Vision

Support: NEI grant 1R01EY02391501A1

Title: Combined neural responses from different domain-specific regions successfully resolve ambiguous perception

Authors: ***M. ROSENKE**[1], N. DAVIDENKO[2], K. GRILL-SPECTOR[1], K. S. WEINER[3]; [1]Stanford Univ., Stanford, CA; [2]Univ. of California, Santa Cruz, Santa Cruz, CA; [3]Psychology, Univ. of California, Berkeley, Berkeley, CA

Abstract: Humans categorize objects remarkably fast. Prior research shows that neural responses within a single region are correlated with categorical judgments of visual stimuli, which likely contributes to this behavior. However, it is presently unknown if not just one, but several functional regions in cortex may work together to perform categorical judgments. Here, we use regions that subserve face- and body perception in human ventral temporal cortex (VTC) to test if and how responses from both types of regions contribute to categorical judgments of ambiguous stimuli. We generated a novel set of parameterized silhouette stimuli that spanned a continuous morph space between faces and hands, while controlling for low-level image properties. We defined stimuli at 5 morph levels, ranging from fully face-like (level-1) to fully hand-like (level-5), and behaviorally calibrated intermediate (level-3) stimuli to appear equally face-like and hand-like in a large group of participants (N>60). Using these stimuli, we conducted two types of experiments in 14 independent participants: (i) an fMRI block-design experiment during which we measured mean responses in face- and body-selective regions in VTC and (ii) a behavioral experiment in which subjects categorized the morphed stimuli. This approach allowed us to examine the relationship between neural responses and behavioral categorization. We used a linear regression model using mean responses of face- and body-selective regions as inputs to predict behavioral categorization that was measured independently outside the scanner. We report three main findings. First, cortically adjacent face- and body-selective regions in VTC illustrate different response characteristics to face-hand morphs: responses were highest for morphs that were weighted >50% of their preferred categories and steadily declined for morphs that were weighted >50% of their nonpreferred category. Second, a linear model relating perceptual categorization to neural tuning of either a face- or body-selective region explains a significant portion of the variance in categorization performance (R^2: .35 - .54). Third, a linear combination of neural responses of face- (β=.31) and body-selective (β=-0.22)

regions explains significantly more variance (0.83±.04, R^2±SE, Bonferroni corrected $p<0.05$), and is able to predict human categorization judgements (cross-validated R^2= .70±.16) in a left-out subject. Together, these findings support the idea that the combined neural responses of regions selective for different domains more accurately explains human categorical judgements than neural responses from one category-selective region alone.

Disclosures: M. Rosenke: None. **N. Davidenko:** None. **K. Grill-Spector:** None. **K.S. Weiner:** None.

Poster

488. Representations of Objects

Location: Hall A

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Program #/Poster #: 488.25/M20

Topic: H.02. Human Cognition and Behavior

Support: NRF-2017R1D1A1B03028539

Title: The role of low-level visual properties in rapid snake detection of human observers

Authors: *T. KIM, D. KWON, H.-K. PARK, D.-J. YI;
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Abstract: For primates, the ability to rapidly detect life-threatening stimuli is crucial for survival and reproduction. The presence of threatening stimuli would put evolutionary pressure on primates, leading them to develop a dedicated mechanism for responding to ecological threats. According to the Snake Detection Theory (SDT; Isbell, 2009), because snakes have been prevalent threats to primates, the competition for survival against snakes have inadvertently contributed to the evolution of the visual system of primates. In support of SDT, it has been found that neurons in the pulvinar of monkeys exhibit faster and stronger responses to snake images (Le et al., 2013). In addition, human behavioral studies have also reported that snakes are detected faster and more accurately than non-threatening ones. However, the stimuli (e.g., snakes, fearful faces, and flowers) used in these studies differed in terms of low-level visual properties such as color, brightness, and spatial frequency. In the current study, we investigated the role of low-level visual properties in granting prompt awareness of threatening stimuli. We conducted two behavioral experiments using a continuous flash suppression (CFS) procedure designed to prevent conscious awareness of the target stimuli through dynamic masking. Experiment 1 attempted to replicate the findings of previous studies, measuring how rapidly images of snakes, fearful faces and flowers broke suppression and emerged into awareness. Participants viewed images of the stimuli from each category presented under the CFS and reported the location of the stimuli as soon as they detected the image. Dynamic Mondrian masking stimuli were presented to the participant’s dominant eye, while the target images of

each category were presented to the non-dominant eye. Consistent with previous studies, results showed that the breaking time for detecting snakes and fearful faces were shorter than that for flowers. Experiment 2 then tested the effects of low-level visual properties on breaking time, controlling color, brightness, and spatial frequency of stimuli across all categories. As in Experiment 1, fearful faces were detected faster than flowers. More importantly, however, snakes were no better detected than flowers. The current results suggest that low-level visual properties play an important role in allowing awareness of snakes under CFS. (NRF-2017R1D1A1B03028539)

Disclosures: **T. Kim:** None. **D. Kwon:** None. **H. Park:** None. **D. Yi:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.26/M21

Topic: D.07. Vision

Support: Center for Brains, Minds and Machines (CBMM), funded by NSF STC award CCF-1231216
Office of Naval Research MURI-114407

Title: Evidence that recurrent pathways between the prefrontal and inferior temporal cortex is critical during core object recognition

Authors: *K. KAR[1], J. J. DICARLO[2];
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Abstract: Recurrent circuits are critical to the primate ventral stream's ability to rapidly categorize objects. Using large-scale neural measurements, we have recently revealed putative recurrent computation dependent signals in the late-phase responses of the inferior temporal (IT) cortex which lies at the apex of the primate ventral stream hierarchy (Kar et al. 2019, *Nature Neuroscience)* . These neural signals are critical for solving the object identities in specific images that are difficult for non-recurrent deep artificial neural networks (ANNs); enabling the primates to outperform various feed-forward ANNs for such images and further suggesting the criticality of recurrent computations during core object recognition. However, we do not yet know which brain circuits are most responsible for these recurrent computations: circuits within the ventral stream? within IT? outside the ventral stream? all of the above? Our recent results provide a targeted disruption strategy for identifying such critical recurrent circuits. Specifically, disruption of the relevant recurrent circuits should prevent the emergence of an accurate representation of the object solutions for the late-solved images in IT. This will in turn result in larger behavioral deficits for the late-solved images (compared to the early-solved images).

In this study, we used this strategy to test one of the circuit hypotheses. Based on the presence of object-category selective neurons, anatomical projections to and from IT, and overall experimental feasibility, we focused our efforts to asses the role of "the ventral PFC to IT recurrence circuit". We pharmacologically silenced (via muscimol) ~10mm^2 of ventral PFC and simultaneously measured IT population activity (with chronically-implanted Utah arrays) in two monkeys, while they performed a battery of core object recognition tasks on our previously bench-marked images. Our results show that muscimol injections (~5 μl) in ventral PFC produced a significant behavioral deficit that is correlated with the object solution times (larger deficits for images with higher solution times). In addition, ventral PFC inactivation also reduced the quality of the late-phase IT population decodes. Interestingly, the late-phase IT neural activity after muscimol injection was better explained by a feed-forward ANN compared to the no-muscimol condition. Taken together, these results imply that PFC is a critical part of the recurrent circuity underlying the production of explicit object representations in IT, used for core object recognition behavior.

Disclosures: K. Kar: None. **J.J. DiCarlo:** None.

Poster

488. Representations of Objects

Location: Hall A

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Topic: D.07. Vision

Support: NIH Grant R01 EY-027023
NIH Grant R01 EY-018839
NIH ORIP RR-00166

Title: Comparing simple invariances in V4 to those in a deep neural network

Authors: *W. BAIR, A. W. BIGELOW, D. V. POPOVKINA, D. A. POSPISIL;
Biol. Structure, Univ. of Washington, Seattle, WA

Abstract: Invariance is a central concept in vision - it describes the ability to maintain a similar representation of an object in spite of large changes in appearance on the retina. Examples of invariance range from simple to complicated-from contrast invariance, to translation and viewpoint invariance for complex objects. Quantifying simple invariances may provide a useful way to compare network representations at a fundamental level, and here we compare units in a deep CNN (AlexNet) to V4 neurons in terms of fill-outline invariance, which we recently tested in vivo (Popovkina et al., 2019, J Neurophysiol), and we examine ON-OFF invariance in the CNN because it is related to fill-outline invariance. Popovkina found that most V4 neurons did not maintain the same shape preferences when simple filled shapes were replaced by outlines of

the same shapes, thus had weak fill-outline invariance (FOI), whereas corresponding HMax models responded similarly to fills and outlines (high FOI). We recently found that AlexNet contains mid-layer units that provide very good models of V4-like translation-invariant shape selectivity (Pospisil et al., 2018, eLife), better than the HMax model, and wanted to test whether a CNN would have high FOI like HMax, or low FOI like V4. We presented the same shapes used to test V4 (Pasupathy & Connor, 2001) to the CNN units in four forms: filled or outline crossed with ON (white on black) or OFF (black on white), testing a wide range of stimulus size and outline thickness. We found most CNN units had strong invariance for shape selectivity across the 4 conditions (fill, outline, ON & OFF), and that these invariances were stronger in a trained network than in an untrained network. However, some units had weak fill-outline invariance, and we used visualization techniques to assess how the selectivity of such outliers differed from the mode. We found that low FOI units in middle layers tended to encode surface features, e.g., color, texture, or smooth gradients, in addition to shape, whereas high invariance units were dominated by shape selectivity. Such joint selectivity for form and texture is consistent with V4 physiology. In deeper layers, strongly outline or fill preferring units subserved specific categories with training examples dominated by outlines or filled forms, e.g., the stethoscope unit preferred outlines and had low FOI. We will report how simple invariances in the CNN depend on layer depth, stimulus size, outline thickness, and training. Our results suggest that CNNs are largely unlike V4 in terms of invariant shape selectivity, yet further analysis of CNN units with low FOI may provide insight into circuits that integrate boundary and surface information.

Disclosures: W. Bair: None. **A.W. Bigelow:** None. **D.V. Popovkina:** None. **D.A. Pospisil:** None.

Poster

488. Representations of Objects

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 488.28/M23

Topic: D.07. Vision

Title: Visualization of neural representations using generative adversarial networks

Authors: *K. MALAKHOVA;
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Abstract: Neurons in the higher-level areas of the visual system respond to complex stimuli, such as faces, body parts, tools. However, the representational space encoded by the cells in the latest stage of visual processing is not clear yet. In this study, we show how deep learning visualization techniques can be applied for the visualization of neurons in the visual system. Using Deep Neural Networks (DNNs), we model a neural response of 140 cortical columns

recorded in the inferior temporal cortex of two macaque monkeys (Sato et al., 2013). The architecture of the model consists of convolutional blocks followed by fully connected layers. The output of the model is a prediction of the response of an individual column for a given visual stimulus. The model has a correlation coefficient of up to 0.86 in predicting the firing rate of certain cortical columns (with a mean of 0.74 for all columns). At the second stage, we visualize the trained model. Representations encoded by the model's neurons are explored using Generative Adversarial Networks (GANs). GANs aim to produce an image which causes a strong activation in a selected neuron. We compare several generative approaches resulting in visualizations of different types: (1) conditioning GANs with prior information to produce natural-looking images (Nguyen et al., 2017), (2) GANs with weak prior or without it, which may output adversarial examples (Olah et al., 2017). The results are compared to a classic approach where images from existing dataset ranked by their evoked response (a tuning curve). We show that the prior distribution obtained during GAN training procedure plays a crucial role in the ability of a generative network to produce images that evoke a high response in the model of the high-level visual areas. We also show how generative techniques can be used in real-time experiments to overcome the constraints introduced by the size of an experimental dataset, which is particularly valuable for the experiments with strictly limited recording time.

Disclosures: K. Malakhova: None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.01/M24

Topic: D.07. Vision

Support: DFG KO 3918/5-1

Title: Getting to know you - Multivariate pattern decoding of EEG data shows how identity representation is born in the human brain

Authors: G. KOVÁCS[1], G. AMBRUS[1], C. EICK[1], D. KAISER[2];
[1]Dept. Biol. Psychol. Cog. Neurosci, Friedrich-Schiller-University of Jena, Jena, Germany;
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Abstract: The identification of someone is one of the most important tasks of the ventral visual system. Recently, we have shown that face identity information emerges gradually (between 100 and 400 ms post-stimulus onset) for famous familiar faces with an increasing degree of invariances (Ambrus et al, Cerebral Cortex 2019 Feb 7). Here we describe the results of a series of experiments where we used EEG and multivariate analysis techniques to elucidate the birth of these representations. Human participants viewed a set of highly variable face images of 4

unfamiliar persons before and after (1) a brief perceptual learning task, or (2) an extensive, several-day long personal familiarisation phase. Although face-matching performance was higher for the trained as compared to the novel identities after the perceptual training (1), multivariate representational similarity analysis did not reveal any difference between the learned and novel faces post-learning. The personal familiarisation (2), on the other hand led to a strong signal of familiarity, starting around 200 ms post-stimulus onset and a weaker, later (300 ms) and left lateralised decoding of learned identities. Our results suggest that a far longer and intensiver familiarisation training is necessary to create the robust identity representations, which are typical for the faces of famous persons than previously thought.

Disclosures: **G. Kovács:** None. **G. Ambrus:** None. **C. Eick:** None. **D. Kaiser:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.02/M25

Topic: D.07. Vision

Support: NIH Intramural Research Program

Title: Temporal dynamics of dorsal and ventral visual stream interaction during configural face processing

Authors: ***K. D. RANA**[1], A. C. DEL GIACCO[1], V. ZACHARIOU[2], L. G. UNGERLEIDER[1]; [1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Cognitive Neurosci. of Aging Lab., Univ. of Kentucky, Lexington, KY

Abstract: Of critical importance to human social interaction is the ability to recognize faces. Classically, facial recognition was considered a task relegated to the ventral visual stream, which contains a network of face-selective regions. Recently, Zachariou and colleagues demonstrated that the dorsal visual stream also contributes to the processing of the configural aspects of faces (Zachariou et al, 2016), which involves perceiving the spatial relationships between facial features. In this study, we used magnetoencephalography (MEG) to quantify when and how the dorsal and ventral streams interact to identify faces with configural differences. Subjects (n=18) viewed sequences of faces organized into 20 blocks of 21 faces each. Their task was to respond via button press if the currently viewed face was different from the face presented immediately before it. The faces could differ in either a configural or featural manner, with the difference type fixed for each block. Within a block, 50% of the trials were difference trials and 50% were not. Difficulty between configural and featural conditions were matched by accuracy separately for each participant. We identified two face-selective regions (lateral occipital cortex (LO) and fusiform gyrus (FG)) and one dorsal-stream region (intraparietal sulcus (IPS)) using functional

localizers in MEG. Dynamic Granger Causality (DGC) analysis revealed a network of communication between LO, FG, and IPS significantly higher than the measured DGC during baseline recordings while correcting for false discovery rate (signed rank test, $z > 2.918$, $p < 0.002$). A feedforward functional connection between 100 to 240 ms from LO to FG was present in both configural and featural trials but was significantly weaker in configural trials (signed rank test, $z = -3.136$, $p < 0.001$). For configural trials only, a bidirectional connection was found between LO and IPS at the same time as the LO to FG connection and a later IPS to FG connection was found between 220 to 310 ms. Our results thus suggest a critical role for IPS in configural face processing, first engaging LO as early as 100 ms and then later engaging FG at 220 ms.

Disclosures: K.D. Rana: None. **A.C. Del Giacco:** None. **V. Zachariou:** None. **L.G. Ungerleider:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.03/M26

Topic: D.07. Vision

Support: DFG (TH 425/12-2)

Title: Beyond the uncanny valley: Naturalistic dynamic monkey head avatar elicits behavioral reactions comparable to videos of real monkeys

Authors: *R. SIEBERT[1,3], N. TAUBERT[2,1], S. SPADACENTA[1], P. W. DICKE[1], M. A. GIESE[2,1], P. THIER[1];
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Abstract: Natural faces and especially facial expressions provide crucial social information not only for humans, but also for monkeys. Humanoid robots or computer avatars are evaluated as more positive the more human-like they are, but very realistic synthetic agents are perceived as unsettling by humans, a phenomenon known as the “uncanny valley effect”. This uncanny response has been shown to also exist in macaque monkeys. We aimed at generating a standardized monkey head avatar capable of producing natural facial expressions (fear grin, lip smacking, threat and neutral) that does not fall into the uncanny valley. To this end we developed a highly naturalistic moving avatar, animated by motion capture data from monkeys, and, in addition, degraded variants of the avatar of decreasing degrees of realism (furless, grayscale and wireframe avatar heads). We exposed eight adult male rhesus macaques to dynamic and static

clips of all different avatars and to videos of a real monkey and recorded their looking behavior, their facial expressions and various physiological parameters. The monkeys' visual behavior indicates that two of the less realistic avatars, but not the most unrealistic and not the most naturalistic avatar, fall into the uncanny valley. Moreover, the dynamic facial expression of the avatars had a significant effect on the amount of time the monkeys spent looking at the faces, how detailed they explored it and which parts of the faces they focused on. Some monkeys even responded to the avatar videos with reactive facial expressions like lip smacking, fear grinning or signs of agitation. Overall, the results confirm the existence of the uncanny valley phenomenon in monkeys, but show that it can be overcome by using sufficiently naturalistic monkey avatars, which can elicit reactions comparable to videos of real monkeys.

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Poster

489. Faces and Bodies

Location: Hall A

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Program #/Poster #: 489.04/M27

Topic: D.07. Vision

Support: Deutsche Forschungsgemeinschaft (TH 425/12-2)

Title: Changes of the variability of neuronal responses in the posterior superior temporal sulcus of monkeys complement rate-based information on social interactions

Authors: *H. RAMEZANPOUR, M. GÖRNER, P. THIER;
Cognitive Neurol., Hertie Inst. for Clin. Brain Research, Univ. of Tübingen, Tübingen, Germany

Abstract: Neural activity in a well-defined patch in the posterior superior temporal sulcus (the "gaze following patch", GFP) of the human and the macaque monkey brain is strongly modulated when the other´s gaze attracts the observer's attention to objects, the other is looking at (Marciniak et al. eLife 2014; Marquardt et al., eNeuro 2017). Our analysis of average discharge rates of neurons in the monkey GFP indicates that they are involved in two distinct computations: the allocation of spatial attention guided by the other´s gaze vector and the suppression of gaze following if inappropriate in a given situation.
Here we asked if the discharge variability of neurons in the GFP could provide complementary information. To this end, we calculated the Fano factor as a measure of trial by trial discharge variability as a function of time. In the analysis we distinguished GFP neurons into task-selective and unselective ones based on their responses in two behavioral paradigms, requiring gaze following or, alternatively, the need to suppress it and to use facial information on the other´s identity to identify distinct spatial locations resorting to learned associations ("identity

mapping"). Selective neurons were activated by only one of the two tasks, whereas unselective ones were driven by both. Our results demonstrate that information on the other´s gaze and the control signals needed to switch between gaze following and identity mapping influence the variability of pSTS neurons independent of type. Whereas erroneous decisions were typically preceded by an increase of discharge variability, correct decisions were associated with low variability, no matter if the neuron was selective or not. Moreover, the strongest drop in variability occurred on average about 20 ms earlier in gaze following trials than in identity mapping trials, in which monkeys had to suppress gaze following in order to use identity cues for the reallocation of spatial attention.
Unselective neurons cannot contribute to the strength of the population signal responsible for the choice of the correct behavior. However, by reducing their discharge variability, unselective neurons improve the signal to noise ratio, thereby helping to increase the assertiveness of the population vote on the correct behavior. The fact that the decision to follow gaze impacts discharge variability considerably earlier than the decision to suppress it in order to map identity is in line with the notion that gaze following is a fast, domain-specific function whose suppression requires extra processing.
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Disclosures: H. Ramezanpour: None. **M. Görner:** None. **P. Thier:** None.

Poster

489. Faces and Bodies

Location: Hall A

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Program #/Poster #: 489.05/M28

Topic: D.07. Vision

Support: NEI EY 16187
P30 EY 12196

Title: The neurons that mistook a hat for a face: Neuronal responses to visual clutter and ambiguity

Authors: *M. J. ARCARO[1,2], C. R. PONCE[3], M. S. LIVINGSTONE[2];
[1]Psychology, Univ. of Pennsylvania, Philadelphia, PA; [2]Harvard Med. Sch., Boston, MA;
[3]Neurosci., Washington Univ. At St. Louis, Saint Louis, MO

Abstract: Inferotemporal cortex (IT) contains neurons that respond selectively to complex visual images such as faces, hands, and bodies. Such neural tuning is typically probed in highly controlled experiments where stimuli are presented in isolation. However, our typical visual experience is more complex. Here, we explored tuning properties of IT neurons under more

naturalistic conditions.
We recorded from microelectrode arrays implanted in the middle and posterior face patches in two adult monkeys. Tuning was first characterized with a rapid serial visual presentation (RSVP) of 3,000 images. Consistent with prior studies, these neurons responded more strongly to human and monkey faces than to any other image category. We then probed tuning to large naturalistic scenes. To identify scene components that modulated these neurons, we presented each image centered at different positions relative to each neuron's receptive field (RF) such that the neuron responded to all parts of each scene across the experiment. Consistent with results from the RSVP task, we found that in naturalistic scenes neurons responded most strongly when faces, and specifically eyes, were centered within their RFs. However, neurons also responded to non-face images, such as cookies, that contained features typical to faces: dark round things in a tan background. These neurons responded to faces even in highly cluttered scenes. The timing of responses and behavioral measures from subsequent free viewing conditions suggest that face-specific activity emerges fast and is driven by bottom-up facilitation prior to awareness. Strikingly, in conditions of visual ambiguity such as occlusion, these neurons also responded to the region of the image where a face ought to be as predicted by context. e.g., neurons did not respond to a picture of a hat held in a person's hand, but did respond when the same hat occluded the face. The timing of responses suggests that occluded-face activity is driven largely by bottom-up facilitation and local recurrent processes.
Together, our results demonstrate that in naturalistic scenes categorical discriminability of face-selective neurons is retinally specific. Further, these neurons are sensitive not only to features common to faces but also to the context of scenes, particularly in cases of visual ambiguity where face-specific visual stimulation is absent. We propose that visual features are the building blocks for face-selective neurons, and context-dependent responses arise from learning regularities in the environment. In support of this, visual features that co-occur with faces, such as bodies, appear to be critical for contextual responses (Cox et al. 2004).

Disclosures: **M.J. Arcaro:** None. **C.R. Ponce:** None. **M.S. Livingstone:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.06/M29

Topic: D.07. Vision

Support: DFG (TH 425/12-2)

Title: Electrical microstimulation establishes a causal role of the superior temporal gaze-following patch (GFP) in controlling gaze-following and its context dependent modulation

Authors: *I. CHONG, H. RAMEZANPOUR, P. THIER;
Cognitive Neurol., Hertie Inst. for Clin. Brain Res., Tuebingen, Germany

Abstract: In order to identify an object a conspecific is looking at, one must be able to determine his/her eyes and head directions and redirect one's own attention towards said object, thereby establishing joint attention. This process is known as gaze-following, and work in our group has previously shown that a cortical area in the posterior superior temporal sulcus (pSTS), which we have designated the GFP, is recruited for this behavior. Neurons in the GFP provide information on the spatial location of an object of interest under the gaze of another individual, as well as information needed to suppress gaze-following in situations in which it may be inappropriate. In our experiments the need to suppress gaze-following is typically realized by asking the observer to ignore the other´s gaze but to rely on the other´s identity to identify a target, in this case resorting to learned associations between possible targets and identities. To differentiate between the two behaviors, an instruction cue informed the observer whether to follow a conspecific's gaze, or alternatively engage in identity mapping. The target choice was indicated by a saccade to the object selected. Here we report results from experiments in which we deployed electrical microstimulation in the GFP of two male rhesus macaque monkeys to disrupt normal information processing in the patch in order to establish causality. We show that stimulating the GFP disrupted gaze-following if it was instructed, and the stimulation applied in the period in which information on the other's gaze direction and the spatial targets were available. The errors made by the observer were random rather than reflecting a bias for a particular target or a target associated with the seen identity. However, when we shifted the perturbations to the instruction period of the paradigm, the suppression on gaze-following was abolished, and instead identity-mapping became compromised. All in all, our results support a causal role of the GFP in gaze-following. Moreover, they indicate that the GFP is also involved in the executive control of gaze-following, i.e. suppressing gaze-following if inappropriate, by integrating expedient signals contributed by other cortical areas.

Disclosures: I. Chong: None. **H. Ramezanpour:** None. **P. Thier:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.07/M30

Topic: D.07. Vision

Title: Are face processed nonconsciously? Yes, but so are dartboards and alarm clocks: An EEG and b-CFS investigation of nonconscious perception

Authors: H. M. QUILLIAN[1,2], *A. D. ENGELL[1];
[1]Kenyon Col., Gambier, OH; [2]Yale Univ., New Haven, CT

Abstract: The social and evolutionary importance of faces has led to the proposal that they are detected by the visual system even when the viewer is not consciously aware of their presence. Here, we report two experiments that investigate this notion. EXP 1: In this EEG experiment, we used a novel combination of continuous flash suppression (CFS) and steady-state evoked potentials. The former is a well-known paradigm for leveraging interocular rivalry to present stimuli nonconsciously, whereas the latter is an EEG approach that affords greater SNR than prior ERP studies. 23 participants viewed a continuous stream of images, each presented for 167 ms (6 Hz). Within the stream, an "oddball" was presented as every fifth image (1.2 Hz). In our primary experimental condition, "frequent" images were objects and oddball images were faces. In a second condition, frequent images were scrambled objects and oddball images were objects. When stimuli were presented without CFS (i.e., images consciously perceived) we observed significant power at the oddball presentation frequency, 1.2 Hz, and its harmonics. We predicted that when presented with CFS (i.e., images not consciously perceived) we would observe a similar increase in power for face, but not object, oddballs. However, we did not observe any such increase and therefore did not find EEG evidence that faces were being processed outside of awareness. Paradoxically, participants became aware of the stimuli significantly faster in the face oddball condition than in the object oddball condition. Breakthrough time (b-CFS) differences are thought to imply nonconscious processing, but we observed no concomitant face-selective neural signal. EXP 2: One possible reason for the contradictory results would be if the b-CFS difference was due to a low-level visual feature, such as the high curvilinearity of faces, rather than high-level category membership. To test this, we compared the b-CFS for 37 participants who each viewed four different conditions in which the frequent images were always scrambled objects. The oddball images were either faces, objects, highly rectilinear objects (e.g., chess board), or highly curvilinear objects (e.g., dartboard). Consistent with the behavioral results of EXP 1, b-CFS for faces was significantly faster than for objects. Critically, b-CFS for curvilinear objects was also significantly faster than for objects and rectilinear objects, and did not differ from faces. The results of these experiments suggest that any privileged access faces have during nonconscious perception is owed to their relatively high curvilinearity and not to high-level category membership (i.e., the "specialness" of faces).

Disclosures: H.M. Quillian: None. **A.D. Engell:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.08/M31

Topic: D.07. Vision

Support: NIH Grant R01EY16187

Title: Visualizing the evolving selectivity in macaque visual cortex using a generative adversarial network

Authors: *P. F. SCHADE[1], W. XIAO[2], T. S. HARTMANN[1], M. S. LIVINGSTONE[1]; [1]Neurobio., Harvard Med. Sch., Boston, MA; [2]Harvard Univ., Boston, MA

Abstract: Neuronal stimulus selectivity arises as a consequence of inputs from other neurons. Short and long-range inputs create complex tuning and dynamic response profiles. From the earliest stages of the macaque visual system, neurons have complex spatiotemporal response patterns, with transient selectivity differing from later sustained selectivity, reflecting the slight delay of lateral and feedback contributions. To investigate the temporal dynamics of responses in macaque visual cortex, we used a genetic algorithm (XDREAM; Ponce, Xiao, Schade et al. 2019), guided by neuronal responses in temporally constrained windows, to search a latent space in a generative adversarial network for images that could drive neuronal responses with predetermined temporal response patterns. The algorithm searched in parallel for images that could cause individual neurons or small populations of neurons in V1, V2, V4, posterior inferotemporal cortex (IT) or central IT to respond selectively with a transient, sustained, or delayed firing pattern. Starting with achromatic textures, complex images and textures evolved that caused neurons to respond maximally within the chosen temporal window. These experiments revealed known temporal dynamic properties of V1, such as delayed surround suppression, thought to arise from local lateral connections and intra-areal recurrent feedback. Similar temporally distinct response profiles were evoked in IT. In classically defined face-patches PL and ML, the algorithm evolved images with features that resembled faces when using the sustained response for the evolution, but those features were only infrequently present when using the transient response. For the algorithm to find images that elicit high firing rates, there must be information in both the high and low firing rate regimes of these neurons. Therefore, even in IT, all gradations in firing rate contain information about the feature selectivity of a neuron. This ‘tuning all the way down’ in feature space argues for a distributed representation over the entire macaque visual system. Since the visual system is a processing hierarchy, and V1 and IT are only stages within the hierarchy, the kinds of computations that take place in these areas are likely not qualitatively different. Given this, we may have a glimpse of how recurrent activity in higher order cortex supports recognition.

Disclosures: P.F. Schade: None. **W. Xiao:** None. **T.S. Hartmann:** None. **M.S. Livingstone:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.09/M32

Topic: D.07. Vision

Support: ERC Grant ERC-StG-284101
C14/16/031
FWO Marie-Curie fellowship (B. Ritchie)
Hercules

Title: The nature of category selectivity in the ventral visual pathway

Authors: B. RITCHIE, J. BOSMANS, S. SUN, K. VERHAEGEN, A. ZEMAN, ***H. P. OP DE BEECK**;
KU Leuven, Leuven, Belgium

Abstract: The end stage of the ventral visual pathway is characterized by a category-based representation of objects. The nature of this category selectivity is ill-understood. Two major factors emerge from the literature. On one hand, the search for category-selective regions with maximal selectivity has shown the presence of a few such regions for a small minority of categories, such as faces and other body parts (Downing et al., 2016). On the other hand, analyses of the distributed pattern of selectivity across occipitotemporal cortex at large have emphasized the dominance of more encompassing dimensions, in particular the animate-inanimate continuum (Connolly et al., 2012; Kriegeskorte et al., 2008; Sha et al. 2015). Here we present an experimental paradigm that is designed to dissociate the two hypotheses. Animate stimuli consisted of a single close-up face and full-body image of 24 animals from different biological classes (48 images total). These were contrasted with images of natural objects. We collected data for behavioral tasks including judgments for pair-wise face and body similarity, and similarity to human faces and bodies. The responses from these tasks were used to construct dissimilarity matrices (DM) to perform representational similarity analysis, and compared with DMs constructed from neural responses from ventral pathway regions selective for objects, faces, and bodies measured with human fMRI (N = 15). We found that while the face-body division dominated the organization of the pathway, a weaker animacy continuum effect was also observed. The animacy continuum effect was also preserved when analyzing face and body responses separately. Overall, categorical object representations are primarily organized in terms of similarity to body part templates, and the apparent organization for animate-inanimate is mostly a secondary consequence.

Disclosures: H.P. Op de Beeck: None. **J. Bosmans:** None. **S. Sun:** None. **K. Verhaegen:** None. **A. Zeman:** None. **B. Ritchie:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.10/M33

Topic: D.07. Vision

Support: Intramural Research Program, NIMH

Title: Anterior face patch neurons display characteristic tuning to specific facial parts

Authors: *E. N. WAIDMANN[1], K. W. KOYANO[1], J. J. HONG[1], B. E. RUSS[2,1], D. A. LEOPOLD[1];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Nathan S. Kline Inst. For Psychiatric Res., Orangeburg, NY

Abstract: The macaque inferotemporal cortex contains clusters of neurons that are visually selective for faces. Neurons in anterior medial (AM) and anterior fundus (AF) face patches are both thought to be tuned to particular facial identities, but it has not yet been established which facial parts, if any, are critical for the observed identity selectivity. Using a 'face parts swapping' stimulus paradigm, we asked how information about image components of the face, body, and scene are reflected in the responses of neurons in the AM and AF face patches. We decomposed ten photographs of monkeys into constituent body, outer face, eyes, and mouth parts. We then recombined these parts into photorealistic hybrids of the internal face (eyes + mouth), head (internal face + outer face), monkey (head + body), and whole scene (monkey + background scene) stimuli. Using chronically implanted microwire brush arrays, we recorded the responses of individual cells in response to combination stimuli and isolated component parts (1,350 stimuli total). Many cells demonstrated strong tuning to a select set of individual parts. A subset of cells displayed a preference for only one of the two parts in a category pair during the hybrid stimuli recombination, and these cells did not show major response changes when combined with the non-preferred part. Another subset of neurons, often found in AF patch, showed tuning to both image parts within select swapping categories. For these cells we tested whether the response to hybrid images could be predicted by the summation of responses to parts alone. The neurons tended to show positive correlation between expected (summed responses to isolated parts) and observed response to hybrid stimuli, suggesting additive computation of individual parts. These results suggested that anterior face patch cells are dedicated to only one or two specific features of the face, rather than whole facial identities.

Disclosures: E.N. Waidmann: None. **K.W. Koyano:** None. **J.J. Hong:** None. **B.E. Russ:** None. **D.A. Leopold:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

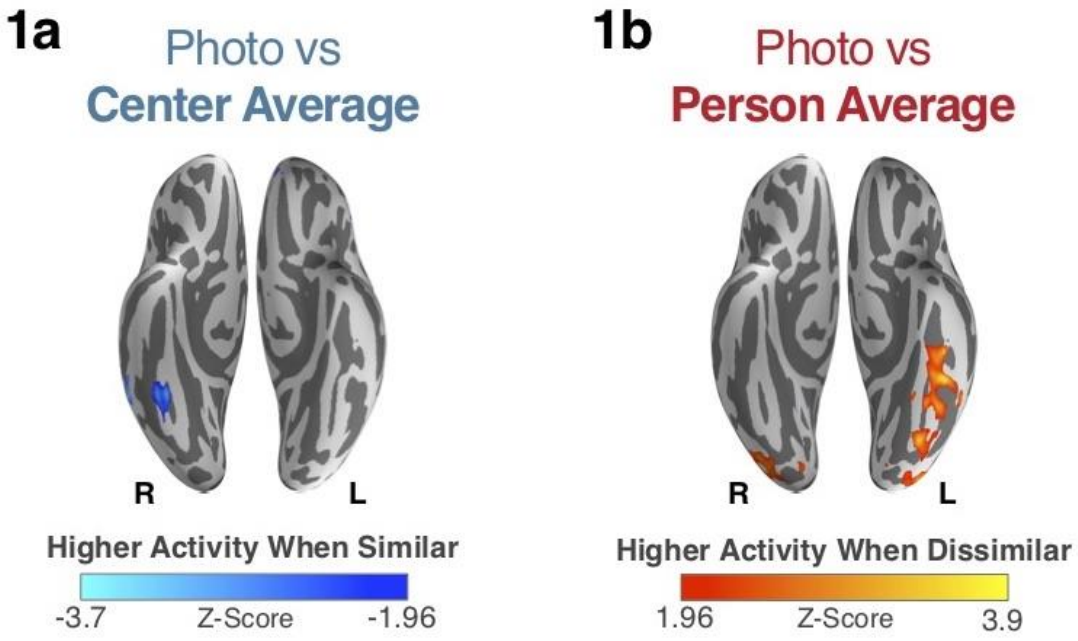
Program #/Poster #: 489.11/M34

Topic: D.07. Vision

Title: Familiar face recognition as deviations from average faces

Authors: Z. SHEHZAD[1], ***G. MCCARTHY**[2];
[1]Columbia Univ., New York, NY; [2]Yale Univ., New Haven, CT

Abstract: We are highly accurate at recognizing familiar faces even with large variation in visual presentation due to pose, lighting, hairstyle, etc. The neural basis of such within-person face variation has been largely unexplored. Building on prior behavioral work, we hypothesized that learning a person's average face helps link the different instances of that person's face into a coherent identity within face-selective regions within ventral occipitotemporal cortex. To test this hypothesis, we measured brain activity using fMRI for eight well-known celebrities with 18 naturalistic photos per identity. Each photo was mapped into a face-space using a neural network where the Euclidean distance between photos corresponded with face similarity. We confirmed in a behavioral study that photos closer to a person's average face were judged to look more like that person. fMRI results revealed hemispheric differences in identity processing. The right fusiform face area (FFA) encoded face-likeness with brain signal increasing the closer a photo was to the average of all faces (Fig 1a). This suggests that the right FFA matches each face against a template to signal how much the stimulus looks like a face. In contrast, the left FFA and left anterior fusiform gyrus (aFus) encoded person-likeness with brain signal increasing the further a photo was from the person's average face (Fig 1b). This suggests that the left FFA and aFus processes an identity error signal that indicates how much a face looks (un)like that person. Our results encourage a new consideration of the left fusiform in face processing, specifically for within-person processing of face identity.



Disclosures: **Z. Shehzad:** None. **G. McCarthy:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.12/M35

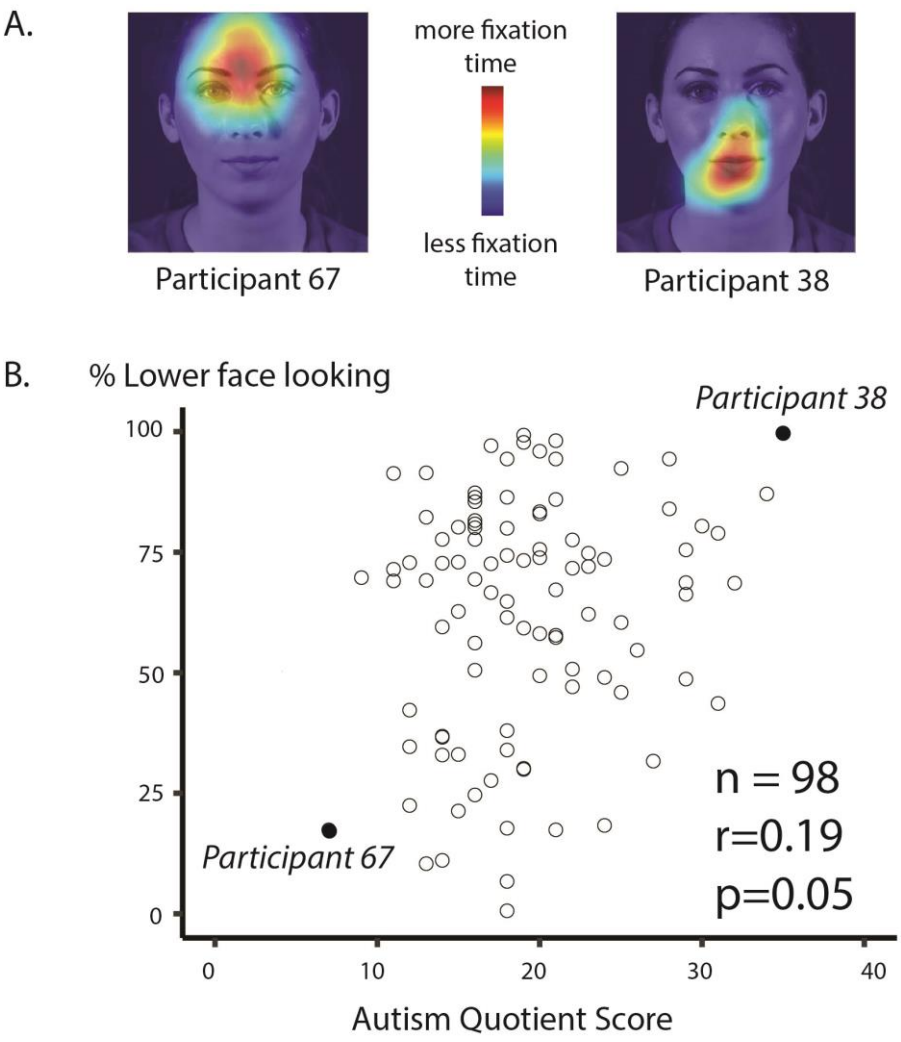
Topic: D.07. Vision

Support: NIH Grant R01NS065395 to M.S.B.
DFG Grant RE 3593/1-1 to J.R.

Title: A relationship between autism quotient score and face viewing behavior in healthy adults

Authors: *K. WEGNER-CLEMENS, J. RENNIG, M. S. BEAUCHAMP;
Neurosurg., Baylor Col. of Med., Houston, TX

Abstract: Humans viewing faces make stereotyped eye movements, with fixations localized to the eye, nose and mouth region of the viewed face. Recently, substantial individual variability in face viewing behavior has been documented: some individuals mainly fixate the eyes while others mainly fixate the mouth (Figure 1A). Inter-individual differences are consistent across stimulus exemplars and testing intervals as long as 18 months but little is known about their origin. Differences in face viewing behavior have previously been linked to clinical diagnoses. In particular, people with autism spectrum disorder (ASD) often avoid fixating the eye region of the face. Based on this observation, we set out to determine whether autistic traits in healthy adults could explain individual differences in face viewing behavior. Autistic traits were measured in 98 healthy adults using the autism-spectrum quotient, a validated 50-statement questionnaire. Face-viewing behavior was measured using two different types of audiovisual movies. Syllable movies had duration 2 seconds and consisted of talkers speaking single syllables ("ba", "ga", or "da") that were identified by the viewer. Sentence movies consisted of talkers speaking complete sentences (mean duration 22 seconds) with no task. For both types of movies, there was a correlation between autism quotient score and percent of time fixating the lower half of the face ($r=0.19$, $p=0.05$ for syllable movies and $r=0.31$, $p=0.008$ for sentence movies). These findings demonstrate that higher levels of autistic traits are linked to avoidance of eye fixations during face viewing in healthy adults.



Disclosures: **K. Wegner-Clemens:** None. **J. Rennig:** None. **M.S. Beauchamp:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.13/M36

Topic: D.07. Vision

Support: NIMH Intramural program

Title: Whole brain fmri reveals the neural correlates of face pareidolia in monkeys

Authors: *J. TAUBERT[1], S. G. WARDLE[2], S. KUMAR[1], C. T. JAMES[1], E. KOELE[3], A. MESSINGER[4], L. G. UNGERLEIDER[5];
[1]The Natl. Inst. of Mental Hlth., Bethesda, MD; [2]Lab. of Brain & Cognition, [3]NIMH, NIH, Bethesda, MD; [4]Lab. of Brain and Cognition, Natl. Inst. of Mental Hlth., Bethesda, MD; [5]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: The common illusion of faces in inanimate objects, known as face pareidolia, can be considered an error of face detection. Previously we have shown that rhesus macaques (*Macaca mulatta*) perceive illusory faces in the same images (e.g. eggplant, bell pepper, coffee) that humans do (Taubert et al., 2017), demonstrating that the experience of face pareidolia is not unique to humans. Here, we used a functional MRI paradigm previously used in humans (Wardle et al., 2017) to investigate the neural correlates of face pareidolia in the macaque brain. We used contrast agent enhanced functional imaging in awake macaques (Experiment 1, *N*=4; Experiment 2, *N*=2) in a 4.7T Bruker vertical MRI scanner. The on-off block design used the same paired stimuli as the human experiment: examples of face pareidolia and matched objects belonging to the same category. In Experiment 2, we also included real faces as a category of stimuli in the design. Place-selective, object-selective and face-selective voxels in temporal cortex were defined in all 6 subjects based on independent data from a functional localizer experiment. In Experiment 1, we tested subjects previously exposed to the experimental stimuli. The results indicated that object-selective voxels responded less to objects with illusory facial features than to objects with no illusory facial features. In Experiment 2, we tested two new subjects never exposed to examples of face pareidolia. Not only did we replicate the results of Experiment 1, the data further indicated that face-selective voxels in the ventral visual system respond more to illusory faces than to non-face objects; the magnitude of this effect was largest near the face-selective patches on the lateral edge of the superior temporal sulcus. Face-responsive voxels in the amygdala and face-selective voxels in the frontal cortex also responded more to examples of face pareidolia than to non-face objects. It is noteworthy that the pulvinar was engaged more by illusory faces than real faces. These data reveal that an extensive network of brain regions is activated when facial features are falsely detected in the visual environment, even though the visual characteristics of illusory faces differ markedly from those of real faces.

Disclosures: J. Taubert: None. **S.G. Wardle:** None. **S. Kumar:** None. **C.T. James:** None. **E. Koele:** None. **A. Messinger:** None. **L.G. Ungerleider:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.14/M37

Topic: D.07. Vision

Title: fMRI and MEG reveal the spatial organization and temporal dynamics of illusory face perception in the human brain

Authors: *S. G. WARDLE[1], J. TAUBERT[1], L. TEICHMANN[2], C. I. BAKER[1];
[1]Natl. Inst. of Mental Hlth., NIH, Bethesda, MD; [2]Cognitive Sci., Macquarie Univ., Sydney, Australia

Abstract: The human brain is specialized for face processing, yet we sometimes spontaneously perceive illusory faces in inanimate objects. To understand how the human brain processes illusory faces we used fMRI (N=21) and MEG (N=22) to measure the whole-brain activation patterns in response to human faces, illusory faces, and matched objects without an illusory face in an event-related design. In terms of spatial organization, fMRI cross-decoding analysis revealed that both face-selective FFA and object-selective LO in occipitotemporal cortex were sensitive to the presence of an illusory face, as a classifier trained on the distinction between BOLD activation patterns associated with viewing objects with and without illusory facial features was able to predict the presence of a face in new images. This was not the case for scene-selective PPA, although activity in all three regions could successfully discriminate real human faces from objects regardless of whether they had an illusory face. Examination of the underlying representational structure revealed that illusory faces were represented more similarly to human faces than matched nonface objects were in FFA and LO, but not in PPA. In terms of temporal dynamics, MEG revealed that as quickly as 130ms after stimulus onset the presence of an illusory face in an object could be decoded from MEG activation patterns. Combining fMRI and MEG data showed that the representations of the stimuli measured with MEG from 150-190ms post-stimulus onset correlated with their representations in the FFA measured with fMRI. This suggests the FFA has a role in rapid face detection, even when the facial features are illusory and have visual characteristics markedly different from those defining real faces. Further, MEG revealed that although illusory faces were initially similar to real faces in the brain's representation, by only 260ms following stimulus onset, the illusory faces were treated more like objects than like faces. Overall the results show that illusory faces are processed incredibly rapidly by the human brain. This is consistent with the recruitment of a broadly-tuned template for face detection which privileges sensitivity over selectivity.

Disclosures: **S.G. Wardle:** None. **J. Taubert:** None. **L. Teichmann:** None. **C.I. Baker:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.15/M38

Topic: D.07. Vision

Support: FWO G.00007.12-Odysseus

Title: Neuronal coding of dynamic partial shape views in the body selective patch of the anterior STS

Authors: *A. BOGNÁR, R. VOGELS;
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Abstract: Shapes can be perceived as an integrated whole even if their small parts are presented in succession at the same retinal position. Human fMRI studies suggested that these temporally integrated whole shape identities are coded by the lateral occipital complex. To investigate the neuronal mechanisms, we measured single unit responses in the macaque anterior body patch, presenting animal silhouettes moving behind a narrow 0.48° horizontal or vertical slit in both directions.
Responsive neurons were searched with 70 silhouettes. For each neuron, we selected three shapes with different response strengths for further testing. The slit-viewing trials started with the presentation of a fixation spot for 300 ms on top of a noise background, then a vertical or horizontal empty slit inside the noise pattern was presented 1° in the contralateral field, or under the fixation spot, respectively, for 480 ms. The shape moved behind the slit for 773 ms at 6.2°/s. We used two control conditions: a feature-preserved temporal randomized stimulus presentation in which slit-views of 80 ms duration were presented in a randomized order to eliminate the coherent form percept, and one where the 80 ms slit-views were presented in their correct order.
Single neurons showed diverse response patterns during slit viewing. At the population level, firing rates for the slit-views were lower than for the static whole shapes. The shape selectivity of the static stimuli was preserved for the slit-views. We observed a higher firing rate for the slit-views of the original than for their randomized presentation, but the shape selectivity was also preserved for the latter condition.
SVM classification showed reliable decoding of the shapes for the static and slit-viewing conditions. Classifiers trained on the slit-view responses and tested on whole shape responses showed generalization, but not vice versa. Classifying data temporally binned per motion direction showed a high decoding accuracy when the same features were presented, but low accuracy for non-corresponding views. Generalization between orientations was significant but weaker than between motion directions.
Our results suggest that these neurons respond to slit information of their preferred features, but not encode the whole shapes in a slit-invariant way. The differences between the coherent shape and randomized presentation may result from temporal summation of responses to neighbouring views of effective features, which are presented in succession in the original presentation, while these features may be split or surrounded by ineffective body parts, causing masking effects, in the randomized condition.

Disclosures: **A. Bognár:** None. **R. Vogels:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.16/M39

Topic: D.07. Vision

Support: SBA-2019-4254

Title: Effects of tactile stimulation on face and object perception of face transplant patients and controls

Authors: *E. GÜLBETEKIN[1], S. BAYRAKTAR[1], Ö. ÖZKAN[2], Ö. ÖZKAN[2], H. UYSAL[3], A. U. SENOL[4], Ö. COLAK[5], A. SAVKLIYILDIZ[5], D. KANTAR GOK[6];
[1]Psychology, [2]Dept. of Plastic and Reconstructive Surgery, Med. Faculty, Akdeniz Univ., [3]Fac. of Medicine, Dept. of Neurol., [4]Fac. of Medicine, Dept. of Radiology, [5]Fac. of Engineering, Dept. of Electrical and Electronics Engin., [6]Dept. of Biophysics, Med. Faculty, Akdeniz Univ., Akdeniz Univ., Antalya, Turkey

Abstract: The first aim of the study is to understand the effects of tactile stimulation on face perception. The second aim is to find out if there is any difference between facial trauma patients and healthy controls.Two facial trauma patients (a face transplant patient and a patient who has not been operated yet), 10 controls (5female, 5male).The subjects observed faces while a robotic finger was touching on their faces simultaneously. An object perception task was also used as a control task. Forty faces and 40 non-face objects were presented. In the acquisition stage, a fixation point was presented for 3sec, following a black screen for 4sec and a face was presented for 3sec. The robotic finger touched the subject's left cheek for 3sec while he/she was still observing the face. The same procedure was applied for the object task. After each task, the subjects were tested in a face/object recognition test. During the task and test phases, brain signals were recorded via 64 channel Actichamp EEG and subjects' skin conductance responses were recorded via Arduino-based GSR device. Evoked response potentials (ERPs) were averaged from 200 ms before (−200 ms) to 1000 ms after stimulus onset. ERP components were identified and measured with respect to the average baseline voltage over the interval from −200 to 0 ms. The amplitude was measured at occipital and parietal sites (O1, O2, OZ, P3, P4, P7, P8, PO3, PO4, PO7, PO8, TP9, TP10). Results: We found a face-specific P100 response (150-200ms) at the occipital electrode sites (O2, O4, PO4, PO8) and P300 responses over the electrodes OZ, P4,P8, PO3, PO7, PO8 while the subjects were observing the faces. However, the amplitude was higher over the electrodes O1, PO3, PO7, and PO8 during robotic finger stimulation. GSR results showed that the touch of the robotic finger does not have any significant distractive effect ($p>.05$). The subjects' correct response ratios for faces was lower than their correct response ratios for non-face objects $F(1, 11) =44,55$, $p= .001$. Accuracy was .86 for non-

face objects and .65 for faces. The mean accuracy of facial trauma patients is .73 for non-face objects and .50 for faces. The response time (RT) was also different for the two tasks $F(1, 11) = 10,70$, $p = .007$. (1053,81ms and 1462,51ms for non-face objects and faces respectively). The patients' RT was 933,38ms for non-face stimuli and 1340,13ms for faces. It seems that the patients were fast but not correct. The preliminary results indicated that tactile stimulation of one's own face has a significant effect on the perception of other faces. Behavioral and neural data pointed out that there is a difference in face processing of the patients and the controls.

Disclosures: **E. Gülbetekin:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Akdeniz University Research Grant. **S. Bayraktar:** None. **Ö. Özkan:** None. **Ö. Özkan:** None. **H. Uysal:** None. **A.U. Senol:** None. **Ö. Colak:** None. **A. Savkliyildiz:** None. **D. Kantar Gok:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.17/M40

Topic: D.07. Vision

Support: NIH Grant EY024056
NSF/SL Grant CN-1640914

Title: Is the face schema innate? Evidence from learning faces in the congenital blind

Authors: *L. T. L. LIKOVA, M. MEI, K. MINEFF, S. NICHOLAS;
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Abstract: To address the longstanding questions of whether people blind from birth have an innate face-schema, what plasticity mechanisms underlie non-visual face learning, and whether there are interhemispheric differences in face processing in the blind, we used a unique non-visual drawing-based training in groups of congenitally blind (CB), late-blind (LB), and blindfolded-sighted (BF) adults. This Cognitive-Kinesthetic Drawing approach previously developed by Likova (e.g., 2010, 2012, 2013) enabled us to rapidly train and study training-driven neuroplasticity across a levels of visual deprivation. The five-day 2-hour training taught participants to haptically explore, recognize and memorize raised-line images, and then draw them free-hand from memory, in detail, including the fine facial characteristics of the face stimuli. Such drawings represent an externalization of the formed memory. Functional MRI (Siemens 3T) was run before and after the training. Tactile-face perception activated the occipito-temporal cortex in all groups. However, the training led to a strong, predominantly left-hemispheric reorganization in the two blind groups, in contrast to right-hemispheric in the blindfolded-sighted, i.e., the post-training response-change was stronger in the left hemisphere in

the blind, but in the right in the blindfolded. This is the first study to discover hemispheric lateralization for non-visual face processing. Remarkably, for face perception this learning-based change had a sign inversion: positive in the CB and BF groups, but negative in the LB-group. Both the lateralization and inverse-sign learning effects were specific to face perception, but absent for the control nonface categories of small objects and houses. The unexpected inverse-sign training effect in CB vs LB suggests different stages of brain plasticity in the ventral pathway specific to the face category. The fact that a few days of our training sufficed for the totally-blind-from-birth CB to manifest excellent face perception, and even empathy to the facial expression, implies the presence of a preexisting face schema that can be "unmasked" and reactivated by a proper learning procedure. A rebound learning model and a neuro-Bayesian economy principle are proposed to explain the multidimensional learning effects. The results provide new insights into the Nature-vs-Nurture interplay in rapid brain plasticity and neurorehabilitation.

Disclosures: L.T.L. Likova: None. **M. Mei:** None. **K. Mineff:** None. **S. Nicholas:** None.

Poster

489. Faces and Bodies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 489.18/M41

Topic: D.07. Vision

Support: NIH Intramural Research Program

Title: Intermediate visual features of primes bias trustworthiness ratings of neutral faces

Authors: *A. C. DEL GIACCO, K. D. RANA, X. YUE, M. GHANE, L. G. UNGERLEIDER; Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Recent studies have demonstrated that images of textures comprised of intermediate visual features are sufficient for above chance categorical classification of animacy and elicit a functional effect in the amygdala related to affective content (Long et al. 2018; Zachariou et al. 2018, 2019). Hooker et al. showed that images consisting of threat-related content will color the trustworthiness judgments of subsequently presented neutral faces (Hooker et al, 2011). The present study (n=19) addressed whether intermediate visual features are sufficient to bias trustworthiness judgments of neutral faces. Using an algorithm, adapted from previous studies, we generated textured versions of animal images which removed global shape information but kept intact the original images' varying amounts of curvilinear and rectilinear features (Freeman and Simoncelli, 2011; Zachariou et al. 2018). Subjects were presented a priming paradigm with intact or texturized prime images of animals that varied in: threat content (defined by independent ratings of arousal and valence), and in their intermediate level features

(curvilinearity and rectilinearity). Textures were presented first in the paradigm followed by a high contrast mask and then a neutral face. Participants were asked to rate the trustworthiness of faces on a continuous scale. We used a factorial ANCOVA to measure the effects of the prime image features (valence, arousal, curvilinearity, rectilinearity) and their interaction with the prime type (intact/texturized) on the face trustworthiness judgments. In addition, we performed posthoc correlation tests to assess the direction of bias on the trustworthiness ratings. The results revealed a significant negative bias of trustworthiness rating on the faces when presented primes with low valence, high arousal, and high curvature, but no significant effect of the prime type. This suggests that the texturized prime, with no global shape information, are sufficient to influence trustworthiness judgments of faces.

Disclosures: **A.C. Del Giacco:** None. **K.D. Rana:** None. **X. Yue:** None. **M. Ghane:** None. **L.G. Ungerleider:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.01/M42

Topic: D.07. Vision

Support: R01-EY014989
P30-NS057091
DGE-1069104
R01-MH118487

Title: V4 local field potentials explain shape detection accuracy, precision, and learning

Authors: *E. J. MOORE, K. WEINER, G. GHOSE;
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Abstract: Visual perceptual learning (VPL) is the improvement in the ability to perceive our visual environment, and is essential to how humans and other animals learn to interact with the world. Despite an extensive amount of research, the neural mechanisms responsible for VPL improvements remain controversial. A major challenge has been establishing that physiological correlates of learning is actually responsible for learning, as opposed to merely reflecting changes in the properties or populations responsible. To address this, we employed a perceptual detection task in which neurons in a specific area, V4, have shape driven responses on a scale of tens of milliseconds that are predictive on a trial by trial basis of successful detection. We followed population responses using a chronically implanted electrode while two male subjects (*Macaca mulatta*) learned to detect shapes degraded by noise. Consistent with previous results examining single neurons and neuronal ensembles, we found that, after the course of learning,

variations in the local field potentials of individual electrodes over the course of tens of milliseconds reliably reflected the presentation of degraded shapes and predicted detection decisions made by the animals, and the amplitude of such signals increased after training. Moreover, variations in reliability of shape-related, but not choice-related, signals predicted the significant up-down fluctuations in performance seen over the course of learning in each animal. Together, these results demonstrate that local population signals in area V4 are largely sufficient to explain the timing and reliability of shape detection and how that detection performance increases as a consequence of training.

Disclosures: E.J. Moore: None. **K. Weiner:** None. **G. Ghose:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.02/M43

Topic: D.07. Vision

Support: Marie-Curie 713750
ANR-11-IDEX-0001-02
ANR-10-IQPX-29-01

Title: Sparse deep predictive coding to model visual object recognition

Authors: *V. BOUTIN[1], A. FRANCIOSINI[1], F. RUFFIER[2], L. PERRINET[1];
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Abstract: Convolutional Neural Network (CNN) are popular to model object recognition in the brain. They offer a flexible and convenient framework to model the hierarchical stacking of cortical areas that compose the Visual Ventral Stream. However, CNN suffers from major drawbacks in comparison with realistic models of biological vision. First, CNNs are mostly feedforward and cannot account for the recurrent processing that takes place in the visual cortex. Second, the back-propagation rule used to train CNN involves global learning rules unlikely to be implemented in the brain. Third, the representation generated by CNNs are most often dense whereas those generated by the visual cortex are sparse.
To improve biological plausibility, we propose a new model called Sparse Deep Predictive Coding (SDPC). The SDPC framework takes advantage of the Predictive Coding (PC) theory to model the dynamic update scheme observed in the visual cortex. PC suggests, among other scenarios, that feedback connections from a higher cortical area carry neural predictions to the lower cortical area, while the feedforward connections propagate the unpredicted information (or prediction error) to the higher area. As such, the neuronal state of a layer is recursively updated

towards minimized prediction error. Interestingly, PC approximates the CNN back-propagation into a local learning rule that is assimilable to a biologically realistic Hebbian learning rule. Last but not least, PC includes a local competition mechanism between neurons that performs an 'explaining away' strategy with sparse coding. The SDPC offers a hierarchical and convolutional implementation of the PC theory.
We experimentally assess the SDPC model using two different image databases. First, we quantify how well the SDPC is untangling the visual information contained in a handwritten digits database (called MNIST) under normal and noisy condition. To do so, we train a simple linear classifier to recognize SDPC representation, and we assess the classification accuracy with different level of perturbation. Our results show that the SDPC compete with a similar state-of-the-art model in term of classification accuracy and noise robustness. Second, we point out the qualitative similarities between the biological Receptive Fields (RFs) of the early visual cortex and the features learned by the SDPC model on a face database (called AT&T).
As a result, the SDPC model accounts both for high level behavioral observation (recognition under noisy and normal environment) and electrophysiological results as Gabor-like RFs.

Disclosures: V. Boutin: None. **A. Franciosini:** None. **F. Ruffier:** None. **L. Perrinet:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.03/M44

Topic: D.07. Vision

Support: Whitehall Foundation
NIH Grant 5R01MH116500

Title: Cortical feedback modulation of experience dependent oscillations in mouse primary visual cortex

Authors: *Y. TANG, A. CHUBYKIN;
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Abstract: Experience-dependent plasticity plays an important role in the acquisition of new skills and neural circuit reorganization after injury. Dissecting the circuit mechanisms underlying adult plasticity may help in developing new specific treatments for learning deficits and injury-induced functional impairment. In the mouse primary visual cortex (V1), oscillatory activity emerges after visual perceptual learning, where the mouse passively views a visual stimulus repetitively over days. This oscillation is specific to the spatial frequency of the familiar stimulus and may emerge from the activity of a neuronal ensemble that encodes the spatial frequency of the familiar stimulus. Recent studies have shown that the mouse visual cortex has functionally

specialized regions, among which the lateromedial (LM) visual cortex forms the strongest reciprocal connections with V1. LM feedback connections have been reported to modulate spatial frequency tuning properties of neurons in V1 making them top candidates in modulating the spatial frequency-specific oscillations post-training. To test whether LM modulates experience-induced V1 oscillations, we recorded local field potential (LFP) and single unit activities in V1 with optogenetic inactivation of LM after visual perceptual training. In both LFP and population unit firing, the expression of V1 oscillations was greatly reduced by LM inactivation, with diminished second and third oscillation cycles but almost no change in the visually locked response. LFP frequency band powers were reduced in a wide range of frequencies, which suggests that LM modulates various neural processing pathways that are associated with V1. LM inactivation had broad effects on V1 unit subpopulations, where one subpopulation that fired at multiple cycles had reduced firing at the later cycles of the oscillation and another subpopulation that preferentially fired at the third cycle also showed decreased firing. This preliminary result suggests that LM feedback connections may play a role in familiarity recall in mouse V1.

Disclosures: **Y. Tang:** None. **A. Chubykin:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.04/N1

Topic: D.07. Vision

Support: NIH Grant R01EY020851
Simons Foundation 365004
NSF 1265480

Title: Representations of image identity and image memorability are shaped by different mechanisms in inferotemporal cortex

Authors: V. MEHRPOUR, T. MEYER, ***N. C. RUST**;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: While we are generally very good at remembering the images that we have seen, we systematically remember some images better than others. The neural correlates of 'image memorability' are thought to reside in high-level visual brain areas such as monkey inferotemporal cortex (IT), where the images that evoke the largest magnitude population responses are remembered best. Remarkably, this same signature is also observed in convolutional neural network models trained to categorize objects, where, like the brain, higher layers of these networks are activated more strongly by some images than others, and the

magnitude of network activation correlates with the images that humans and monkeys find most memorable. Together, these results suggest that the representations of image identity and image memorability are tightly linked. Are they shaped by the same neural mechanisms? To investigate this question, we explored the stimulus-evoked dynamics of IT image identity and image memorability representations in data collected as two rhesus monkeys performed a single-exposure visual memory task. We quantified the dynamics of IT image identity representations as the performance of a multi-way, cross-validated linear classifier at determining image identity based on the IT population response measured at different positions relative to stimulus onset. We quantified the dynamics of image memorability as the strength of the correlation between the magnitude of the IT population response and image memorability scores, also as a function of time relative to stimulus onset. We found that image identity and image memorability representations emerged with different dynamics: identity representations emerged earlier and peaked at 140 ms after stimulus onset, whereas memorability representations emerged later and peaked at 220 ms. These dynamics could be attributed to IT population response vectors that emerged with the distinct patterns indicative of identity representations but with similar magnitudes, and only later reflected the magnitude variation indicative of image memorability. Together, these results suggest that representations of image identity and image memorability are shaped by different mechanisms in IT.

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Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.05/N2

Topic: D.07. Vision

Support: FONDECYT Posdoctorado nº3180389
BNI ICM P09-015-F

Title: Searching for a training protocol to exploit residual visual function in low-vision patients: Six sessions of training improves performance in a complex task of facial emotion recognition using peripheral vision in normally sighted subjects

Authors: *M. JURICIC-URZÚA[1,3], E. LORCA-PONCE[1], S. MADARIAGA[1], D. ZENTENO[1], M. VILCHES[3], L. PRATO[1], K. PADILLA[1], J. VARAS[4,5], P. BUSTAMANTE[6,5], J. ARAYA[5], S. NAZAL[5], P. E. MALDONADO[2];
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Abstract: While visually exploring the environment, people centralize objects of interest in the fovea. But when the fovea is damaged, as in many Low-Vision (LV) patients, central vision is lost and is no longer useful for seeing. Patients start using systematically one or more peripheral retinal regions called preferred retinal loci (PRL) to perform visual tasks, centralizing objects to this PRL, which is also accompanied by neuroplastic events as changing the retinotopic map in V1 or re-referencing eye movements to this region instead of the fovea. Moreover, their performance using their PRL in some visual tasks that require high visual acuity, like reading, can be improved by training. But ¿Can we exploit these neuroplastic events and train people in their peripheral vision to improve their performance in more complex visual tasks as facial emotion recognition? We explore this question by training peripheral vision of 8 normally sighted subjects for 6 sessions (6 weeks; 1 session/week) in a facial emotion recognition task while their eyes movements are recorded using an eye tracker. The task consisted of 4 blocks of 10 trials each one. In each trial a face was presented with or without emotion, 15º left to a point of fixation. Subjects were encouraged to maintain their vision in the point of fixation and to recognize whether there is an emotional face and which emotion was displayed. At the initial session, subjects were able to correctly recognize the presence of emotion in about 80% of faces, but they correctly identified the emotion in only 60% of cases. Reaction times in this session were about 2.5 sec. After training, subjects were able to correctly identify the emotion in about 75% of emotional faces and the reaction time for recognizing the presence of emotion was reduce by about 30%. We found training normally sighted subjects improves their performance in facial emotion recognition without affecting fixation stability. These results support the idea that peripheral vision can be trained in order to perform a complex visual task as facial emotion recognition and hint to the necessity to further explore the utility of this training protocol in patients with LV caused by retinal diseases that produce central vision loss.

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Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.06/N3

Topic: D.07. Vision

Support: ERC-StG-2017-758898

Title: Decoding memory-specific feedback signals from early visual areas

Authors: *J. ORTIZ-TUDELA[1], J. BERGMANN[2], M. BENNETT[3], L. MUCKLI[2], Y. SHING[1];
[1]Goethe Univ., Frankfurt, Germany; [2]Inst. of Neurosci. and Psychology, Col. of Medical, Vet. and Lif, [3]Ctr. for Cognitive Neuroimaging, Univ. of Glasgow, Glasgow, United Kingdom

Abstract: Predictive accounts of the brain rely heavily on the idea that the human brain stores some form of information from which predictions can be drawn. However, the source and nature of this information still remain largely unknown. We propose that episodic memory may be a candidate source for predictions. In order to test this hypothesis, we use a paradigm that has shown to be suited for isolating predictions fed-back to early visual cortex: by physically occluding portions of scenes it is possible to record activity in non-stimulated regions of the early visual cortex. In a first study, participants were trained with cartoon images depicting common real-world locations that included one key object. In a subsequent session 24 hours later, we used high-resolution fMRI to record activity from the voxels in V1 and V2 responding to the retinotopic region corresponding to the object's location while participants performed an object retrieval task. Critically, these images did not include the target objects. We used multivariate pattern analysis to decode scene and object-specific information. The results show that we were able to reliably detect feedback from the scene contexts. However, we could not detect any object-specific information. In a second study, we aimed at strengthening the perceptual features of our participants' memories for the objects by 1) making the objects more distinct in color and shape, 2) increasing the duration of the study session and 3) including a post-study task that required participants to manually draw the objects in their specific location in the original images. Preliminary results show that classification performance for object-specific information is above chance in the occluded sub-regions of both V1 and V2. We also performed cross-classification between different subsets of scenes paired at study with the same objects to assess the generalizability of common information triggered by different cues. Cross-classification was successful in V1 and V2 suggesting precise reinstatement of the objects in memory. As a next step, we will further explore the layer-specific information profile of these feedback signals in the visual cortex and relate them to activity in distant areas that are critical for episodic retrieval (i.e., hippocampus).

Disclosures: J. Ortiz-Tudela: None. **L. Muckli:** None. **M. Bennett:** None. **Y. Shing:** None. **J. Bergmann:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.07/N4

Topic: D.07. Vision

Support: Simons Center for the Social Brain

Title: Temporal expectation in marmosets

Authors: *T. DRAGOI[1], H. SUGIHARA[1], M. HU[1], J. SHARMA[1], M. SUR[2];
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Abstract: In natural environments, animals continuously use stimuli in specific contexts which help them predict and expect forthcoming events. Expectation is an internally generated state that utilizes prior knowledge of the environment to optimize behavioral responses to changing stimulus contexts. Previous work by our lab and others has shown that humans and macaques utilize prior information such as the probability of an event based on past occurrences, which helps reduce uncertainty and improve performance (Sharma et al. 2003, Summerfield et al. 2006). Expectation in a temporal context has been shown to follow hazard rate measurements of an event's rate of occurrence over time. (Ghose and Maunsell 2003, Janssen and Shadlen 2005). Higher brain areas likely use prior information and feed it back to update motor plans for behavioral adjustments to changing task variables. To uncover if marmosets utilize similar strategies to optimize behavior, we developed an expectation based task in marmosets using an in-home cage training system. Two marmosets were trained to hold off touching a tablet until a visual cue was provided, at which point a touch must be registered. To understand if they used hazard rate to guide expectation in this simple task, we measured reaction times to uniformly varying lengths of time of cue disappearance. Although tested in a less controlled environment, our early results show that marmoset reaction time shortens with longer stimulus duration. The distribution of touches following the disappearance of a cue sharpened over time, with mean latency (0.6s) and full width half maximum (0.021s) decreasing across 3 months of exposure to the task. An uncertainty-based hazard rate model more closely correlated with reaction time when compared to standard hazard rate models indicating that reaction time is sensitive to the uncertainty of upcoming stimulus events. We believe that elapsed time is differentially used to adjust reaction times in response to changing patterns of visual input. Further work will examine the neural underpinnings of stimulus expectation. Specifically, we will use optogenetic and pharmacological manipulations to change balance between cortical excitation and inhibition in local and long range cortical circuits to investigate their role in temporal prediction and expectation. Atypical temporal prediction has been implicated in autism, thus our research has the potential to uncover elements of neural processes in such disorders such as how integration of bottom-up and top down feedback in cortical networks provides contextual processing.
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Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.08/N5

Topic: D.07. Vision

Support: The Laura and John Arnold Foundation
Joan and Irwin Jacobs Innovation Grant

Title: Perceptual scaling improves eyewitness identification

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Abstract: Eyewitness identification has long played a valuable role in criminal investigations and prosecutions. Despite this value, our society has been confronted in recent years with many rank failures of eyewitness testimony. For example, more than 350 people, many serving lengthy prison sentences, have been exonerated in the US because their DNA was found to be incompatible with evidence collected from the crime scene. In approximately 70% of these cases, misidentification by eyewitnesses contributed significantly as evidence for conviction.
It is natural to ask what can be done to improve the "performance" of eyewitnesses, such that they are more likely to identify the culprit and less likely to misidentify an innocent person. A major focus of research on this topic has been the manner in which an eyewitness lineup is presented. The traditional "simultaneous" (SIM) lineup is composed of (typically) six facial photographs shown at the same time. One of the faces is that of the suspect and the others, known as fillers, are of people known to be innocent. The alternative "sequential" (SEQ) lineup involves presenting the photographs one at a time. In both lineup types, witnesses are asked to identify the perpetrator or to reject the lineup if no face matches the memory from the crime scene.
The performance of eyewitnesses under the SIM and SEQ paradigms can be explained as the product of recognition memory, a form of declarative memory retrieval in which a sensory "cue" stimulus elicits the trace of a previous encounter with the stimulus, perhaps in a different form or context. This recognition memory is the internal response of the eyewitness upon which a decision is made. The eyewitness also possesses an internal decision criterion: only signals that meet this criterion lead to identification. Because this recognition process is covert, the overt response ("that's the culprit") confounds the strength of the internal response with the internal decision criterion, leaving the outcome susceptible to unrecognized bias.
We describe a novel lineup procedure that permits estimation of memory strength independent of the decision criterion. This procedure employs a longstanding psychophysical technique called the Method of Paired Comparisons. We find that this approach yields accurate identifications

that are uninfluenced by decision bias. The new procedure reveals structure of eyewitness memory that is inaccessible by traditional lineup procedures, allowing triers of fact to estimate the probative value of testimony proffered by individual eyewitnesses.

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Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.09/N6

Topic: D.07. Vision

Title: Visual perceptual learning in the ferret

Authors: *E. L. DUNN-WEISS[1], J. J. ROSS[2], K. J. NIELSEN[1];
[1]Neurosci., Johns Hopkins Univ., Baltimore, MD; [2]Morgan State Univ., Baltimore, MD

Abstract: Visual perceptual learning has been shown to induce plasticity in adults, and even improve visual acuity in the weak eye of adults with amblyopia. Hence, this plasticity is powerful, and clinically relevant. Previous studies have identified putative neural correlates of learning in visual cortex, using fMRI, EEG, and single-unit recordings. However, how learning affects the joint response properties of groups of neurons in visual cortex has received less attention. To begin to investigate this question, we developed a novel head-fixed behavioral setup for ferrets, designed to test them on two-alternative forced-choice tasks. Ferrets are a useful animal model because their visual cortex shares functional properties with non-human primates, including smooth feature maps in primary visual cortex. At the same time, they are amenable to techniques that allow simultaneous recordings from groups of neurons, such as two-photon imaging or recording with multi-site probes. Here, we used the head-fixed setup to first train ferrets to discriminate between gratings rotated clockwise or counterclockwise relative to an oblique reference. Task difficulty could be manipulated by changing the angular distance between the test gratings and the reference. Ferrets were able to perform this task, demonstrated by low lapse rates on the easiest discriminations, and their performance was fit well by standard psychometric functions. After measuring initial psychometric functions, we trained ferrets to discriminate gratings at threshold. Training systematically improved performance, as indicated by less errors on the trained condition and a change in threshold and slope of the psychometric function. In addition to the orientation discrimination task, we found ferrets to be particularly trainable in direction discrimination and motion integration tasks, and continuous training on the latter also resulted in significant performance gains. These results demonstrate that ferrets exhibit the required behavior to be used in learning studies. We are currently incorporating two-photon calcium imaging and electrophysiological recordings using multi-site probes into these

behavioral experiments. These data will provide important insight into learning-induced plasticity at the network level.

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Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

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Program #/Poster #: 490.10/N7

Topic: D.07. Vision

Support: NIH Grant R01EY020851
Simons Foundation 365004
NSF 1265480

Title: Representations of image memory and image memorability are largely non-overlapping in inferotemporal cortex

Authors: *V. MEHRPOUR[1], E. P. SIMONCELLI[2], N. C. RUST[1];
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Abstract: Humans are generally very good at remembering the images that they have seen, although some images are easier to remember than others. Neural correlates of both 'image memory' and 'image memorability' have been linked to inferotemporal cortex (IT), but current accounts of their representations are in conflict. Considerable evidence suggests that image memory is signaled by a reduction in response for familiar as compared to novel images ('repetition suppression'), and lower firing rates correspond to better behavioral memory performance. In contrast, recent findings demonstrate that more memorable images evoke stronger responses in IT, both when images are novel and when they are repeated as familiar, thereby violating the tenet that lower firing rates map to more robust memory behavior. How can these conflicting accounts of image memory and image memorability representations in IT be resolved? To address this question, we analyzed neural data collected from IT as two rhesus monkeys performed a single-exposure visual memory task in which they viewed images and indicated whether they were novel (never seen before) or familiar (seen exactly once). We compared cross-validated linear decoding performance for memory and/or memorability when applied to the intact data and after removing different types of information from the population. Projecting out total spike count information (i.e., projecting the response vectors onto the subspace orthogonal to the (1, 1, 1, ⋯) vector) had a measurable, albeit small, impact on both memory and memorability decoding performance, suggesting that both signals were partially correlated with the total spike count. However, projecting out the linear axis that best captured

either memory or memorability information had minimal impact on the linear decoding performance for the other signal, beyond that attributed to the total spike count. Together, these results suggest that image memory and image memorability occupy partially but largely non-overlapping linear subspaces in IT.

Disclosures: V. Mehrpour: None. **E.P. Simoncelli:** None. **N.C. Rust:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.11/N8

Topic: D.07. Vision

Support: NIH Project 5R00MH099654-05
NSF Award 1633516

Title: Primary visual cortex integrates information across a wide range of time scales and can predict conditional and high-order sequential associations

Authors: *S. KNUDSTRUP, C. JENSEN, B. PRICE, J. GAVORNIK, R. SCHECTER; Biol., Boston Univ., Boston, MA

Abstract: Neurons in V1 are tuned to respond to spatial patterns in the visual scene. Receptive fields quantifying this relationship are well characterized and commonly used as a model to understand how the cortex uses feed-forward processing to extract information. One might think this means we can accurately predict firing patterns of V1 neurons based on an analysis of the spatial content of visual stimulation patterns; one would be wrong. Similar spatial patterns drive different responses when they are presented in an isolated "sciencey" context than they do when presented during a "naturalistic" movie and there is no satisfying explanation for why. A variety of recent studies have shown that movement, spatial location, reward expectation, auditory inputs, attention , and visual experience can all modify evoked activity patterns in V1. A possible explanation for the scope of observations is the idea that cortical circuits perform predictive coding. Implied in this notion is a required ability to represent temporal relationships between otherwise discrete elements of a stimulus or memory. Accordingly, we performed a series of experiments to understand how temporal and ordinal context modulates the activity of V1 circuits. We find that V1 can integrate events occurring seconds apart into a predictive representation, suggesting access to some form of memory persisting well beyond the temporal component of classically defined spatiotemporal receptive fields. We also find that V1 activity can encode conditional probability and higher-order sequential relationships. Assuming it has emerged in the months since abstract submissions closed, we will discuss evidence constraining possible mechanisms. Our results support the idea that predictive coding is a canonical function

of cortical circuits that can be observed and dissected in V1, that complex visual processing occurs at a lower-level in the "visual hierarchy" than usually assumed, and suggest a model system to study the mechanistic bases of implicit learning defects associated with various neuropsychiatric disorders.

Disclosures: S. Knudstrup: None. **C. Jensen:** None. **B. Price:** None. **J. Gavornik:** None. **R. Schecter:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.12/N9

Topic: D.07. Vision

Support: NIH RO1 EY024912
NIH P50 MH103204

Title: Unsigned reward prediction error signals in frontal eye field

Authors: *M. R. SHTEYN[1,2], C. R. OLSON[1,2];
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Abstract: In classic learning theory, surprise is quantified by unsigned prediction error, which determines how much attention is captured by a particular event. Unlike signed reward prediction error, an unsigned prediction error increases with the improbability of an outcome, regardless of its valence. Neurons in the frontal eye field (FEF) are sensitive to reward amount and are involved in the allocation of attention but it is unknown how they respond to surprising outcomes. To address this issue, we trained macaque monkeys in a Pavlovian paradigm requiring them to maintain central fixation while two visual cues were presented in the neuronal receptive field followed by delivery of a reward. Each cue was presented for 300 ms followed by a 600 ms delay. The leading image, depending on its identity, predicted with high probability ($p = 0.83$) delivery of either a large or a small reward at the end of the trial. The trailing image indicated with certainty that the ensuing reward would be either large or small. The information conveyed by the trailing image usually ($p = 0.83$) confirmed, but occasionally ($p = 0.17$) violated, the prediction conveyed by the leading image. In accordance with previous reports, we found that a leading image indicating a high probability of large reward elicited a strong visual response. Likewise, a trailing image predicting large reward elicited stronger activity than a trailing image predicting small reward. The key question of the study was whether a given trailing image would elicit differential firing depending on whether it confirmed or violated the expectation created by the leading image. We found that the strength of the response to the trailing image indeed was

influenced by surprise. Neurons responded more strongly to a trailing image predicting large reward when the probability of large reward was low (p = 0.17) than when it was high (p = 0.83). Similarly, neurons responded more strongly to a trailing image predicting small reward when the probability of small reward was low (p = 0.17) than when it was high (p = 0.83). With appropriate controls we have established these results depend on information about the impending reward and not on the identity or physical salience of the trailing image. In an additional experiment, we show these results depend on whether informative cues appear inside or opposite the receptive field. These results are consistent with the interpretation that cues signaling surprising outcomes capture spatial attention and, in doing so, recruit excitation of FEF neurons with receptive fields encompassing the cue location.

Disclosures: **M.R. Shteyn:** None. **C.R. Olson:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.13/N10

Topic: D.07. Vision

Title: Determination of correlation between eye movement parameters and academic performance of undergraduate senior students

Authors: H. ARGUNSAH BAYRAM[1], M. SAHINER[2], O. HATIPOGLU[1], *M. B. BAYRAM[1], L. ALTINTAS[2], T. SAHINER[3];
[1]Med. Engin., [2]Med. Sch., Acibadem Mehmet Ali Aydinlar Univ., Istanbul, Turkey; [3]Mem. Hosp., Istanbul, Turkey

Abstract: Objective: It was aimed to investigate the correlation between the neurophysiological parameters of the voluntary eye movements controlled by the brain stem connections of the prefrontal cortex, which have an important role in behavioral and learning physiology, and the correlation between the academic achievements of the undergraduate senior students.
Methods: 35 students (n= 35 participants, 19 males and 16 females aged between 20 and 26 years old (m= 24.77; SD= 3.15)) participated in the study, 6 participants' data has been analyzed. All participants' cumulative academic achievement data (Cumulative GPA) were obtained. Each participant completed a two-stage standard Trial Making Test, one stroop test and one visual attention test while wearing Tobii Pro 2 wearable eye tracker. Eye focus mapping, visual attention points and pupil diameter parameters were collected to obtain information about the cognitive functions of the participants. Fixation index (total gaze point/normalized time on task) was defined and correlated with participants' cumulative GPA (M=3.06 SD=0.31) and Felder-Soloman Index of Learning Styles.
Results: The occurrence rate of micro-saccades, which are the small, involuntary eye movements

observed during attempted fixation moments, and pupil diameter variation indicated that the trail making tests were difficult and distinctive as pupil diameter variation was statistically different during these tasks ($p< 0.05$). Participants' fixation indices indicated significantly higher cognitive load during the difficult Trail Making tasks (m=1.46, sd=0.66) compared with the easy attention tasks (m=1.51 SD=0.33) ($p< 0.001$). Pairwise comparisons showed that the difference between the easy and difficult tasks was statistically significant ($p< 0.05$).
Conclusions: The pupil diameter is an indication of cognitive load. In this study, we offered a fixation index to interpret the cognitive load based on measurement of total gaze points during mental trail making and attention tasks. Gaze analysis of the preliminary results indicated that eye movement strategy and fixation index is correlated with the academic achievements of the senior undergraduate students and the learning style index is a distinctive parameter for interpreting the brain function during cognitive tasks.

Disclosures: H. Argunsah Bayram: None. **M. Sahiner:** None. **O. Hatipoglu:** None. **M.B. Bayram:** None. **L. Altintas:** None. **T. Sahiner:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.14/N11

Topic: D.07. Vision

Support: NIH Grant HD088731

Title: Modulation of alpha ERD reflects the acquiring and the emerging structure of novel visual categories

Authors: *J. FISER, S. JELLINEK;
Central European Univ., Budapest, Hungary

Abstract: EEG alpha-band oscillations reflect inhibitory control processes that provide selective access to stored memory, while the onset of alpha event-related desynchronization (ERD) indicates the beginning of recognition/categorization accessing internal conceptual representations. Studies investigating the role of ERD in visual categorization tasks typically use discretely exemplars that are either objects familiar to the observer or have been used in an intensive training into categories prior to the EEG recordings. Thus, it is unclear whether ERD can provide more complex information about the stored representation, such as the dynamics of category formation during learning and the strength of class membership of the given stimulus, beyond simply indicating the onset of the categorization process. We used an altered version of the oddball paradigm typically used for assessing the link between ERD and visual categorization. First, instead of countable individual examples, we used a continuous range of

similar stimuli (human silhouettes) that varied along one parameter, their aspect ratio from thin to fat. Second, we recorded EEG signals throughout the entire learning process, not only after the categories have been formed. Participants' task was to classify the stimulus appearing for 800 ms on the screen as Fat or Thin by pressing a key without receiving any feedback. On each trial, we recorded the participants' choice, RT, and subjective uncertainty as well as their neural responses by a 128-channel high-density EEG setup. Similar to earlier results, we found significant differences in alpha ERD elicited by the frequent and infrequent stimuli [$t(22)=2.88$, $p<.01$]. For stimuli sampled around the category boundary this difference was less articulate early on and became significant only towards the end of the recording sessions. Overall, the amount of ERD was in a remarkably linear agreement with the deviation from the dominant width parameter of the frequent category [$r = -0.98$, $p<.05$]. Thus, alpha-suppression is not only an indicator of the already acquired structure of concepts, but it also allows for reliable tracking the ongoing acquisition of categories, and the strength of the neural response reflects the structure of the internal representation specifying the learned categories.

Disclosures: J. Fiser: None. **S. Jellinek:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

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Program #/Poster #: 490.15/N12

Topic: D.07. Vision

Support: Research Training Group (RTG) 2175 of the German Research Foundation (DFG)
Collaborative Research Center SFB870 of the German Research Foundation (DFG)
Max Planck Society

Title: Single cells in mouse medial prefrontal cortex represent learned rules for categorization

Authors: *S. REINERT, T. BONHOEFFER, M. HÜBENER, P. M. GOLTSTEIN;
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Abstract: Categorization is a learning strategy for forming meaningful groups of objects and experiences. Learning a rule to categorize stimuli allows for generalization of existing associations to novel stimuli, thereby aiding adaptive behavioral responses. In order to study representations of learned rules in the brain, we investigated the medial prefrontal cortex (mPFC) of mice engaged in a rule-based, visual category learning paradigm.
Mice (n=11) were trained to attribute visual stimuli (oriented gratings, varying in orientation and spatial frequency) to a rewarded (go) and a non-rewarded (no-go) category. Every mouse learned to discriminate categories of 9 versus 9 stimuli according to a rule, such as grouping stimuli by

their spatial frequency. This required maximally 48 sessions of 150-200 trials each. All animals were able to generalize the learned rule to 18 novel stimuli upon their first presentation. Changing the underlying rule, such as grouping stimuli by their orientation, required the mice to switch their strategy, which took them 6 to 10 training sessions. Both rapid generalization and the ability to switch strategies show that mice, like primates, are able to form rules for categorization.
In order to investigate the underlying neuronal mechanisms, we followed the activity of individual cells throughout the course of learning with two-photon calcium imaging. After learning, a sparse set of L2/3 mPFC neurons responded selectively to stimuli of one of the two categories (i.e. they showed category selectivity). Neurons representing the 'no-go' category evolved category-selectivity later in the learning process than 'go' category-representing cells. After the rule switch, we observed both a shift in cells' responsiveness to follow the new rule, and recruitment of newly category-selective cells. These results suggest an internal, sparse rule representation in mouse mPFC and they highlight its role in behavioral strategy switches.

Disclosures: **S. Reinert:** None. **T. Bonhoeffer:** None. **M. Hübener:** None. **P.M. Goltstein:** None.

Poster

490. Visual Learning, Memory, and Categorization

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Program #/Poster #: 490.16/N13

Topic: D.07. Vision

Support: Collaborative Research Center SFB870 of the German Research Foundation (DFG)
Max Planck Society

Title: Learning of visual categories is associated with enhanced feature representations in a subset of mouse visual cortex areas

Authors: *P. M. GOLTSTEIN, S. REINERT, T. BONHOEFFER, M. HÜBENER;
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Abstract: Associative memories are thought to be stored in a distributed network that can extend across multiple brain regions. However, it is unclear if and how far a high-level neuronal representation of abstract knowledge traces all the way back to early cortical sensory areas. Here we investigate whether perceptual and semantic features of a learned higher-order association (visual categorization) are already represented at the first stages of visual information processing in the mouse neocortex.
We defined two visual stimulus categories by diagonally dividing a two-dimensional stimulus

space consisting of 42 gratings that systematically varied in orientation and spatial frequency. Mice learned discriminating two initial stimuli, one of each category, during five to six daily sessions in a touch-screen behavioral chamber. Over the next six to eight sessions we introduced information-integration categories encompassing all stimuli in a stepwise manner. Mice generalized stimuli within the same category, while stimuli of different categories were discriminated above chance (>70% correct) according to individually learned category boundaries. Categorization was contingent on neuronal activity in visual cortex and depended partly on the retinotopic position of the visual stimulus, suggesting a role for visual areas in representing the learned associations.
Long-term two-photon calcium imaging revealed that after learning, neurons in primary and higher visual areas of the mouse started responding to task components other than the visual stimulus. By fitting an encoding model, we addressed the fine structure of stimulus-specific responses. This revealed that neurons in V1 and higher areas RL, LI and POR showed an overall increase in category selectivity, which depended on changes in both stimulus feature- and category tuning. These results support the view that associative memories percolate throughout the brain, with learning in early stages shaping perceptual representations to support the semantic content.

Disclosures: **P.M. Goltstein:** None. **S. Reinert:** None. **T. Bonhoeffer:** None. **M. Hübener:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.17/N14

Topic: D.07. Vision

Title: The interaction of category representation and spatial frequency in the macaque inferotemporal cortex

Authors: *B. KARAMI[1], R. KOUSHKI[1], E. REZAYAT[1], F. SHAKERIAN[2,1], A.-H. VAHABIE[1], M.-R. A. DEHAQANI[3,1];
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Abstract: The information carried by different spatial frequency (SF) has long been recognized to represent in a coarse-to-fine sequence. The visual system uses the combination of global and local features, which are carried by low SF (LSF) and high SF (HSF) respectively, to facilitate the processing of the upcoming stimulus. To understand better the mechanistic role of SF processing in temporal dynamics of category representation, we examined neural responses of

the inferior temporal (IT) cortex of macaque monkeys viewing SF filtered face and non-face stimuli with two different exposure times (fast trials: 20ms and slow trials: 200ms). The stimuli were six faces and three inanimate objects and each of which had been filtered in five frequency ranges (band-pass SF filter). In addition, for all the stimuli, corresponding phase-scrambled images were generated. All stimuli were equalized to have same luminance and contrast. We directly addressed spatiotemporal dynamics of object and face representation by investigating how the network of IT neurons processes distinct SF over time. We applied a combination of encoding and decoding methods to the single and population of recoded neural data to explore the role of SF coding properties in IT category representation. Consistent with the coarse-to-fine nature of perception, we found an earlier representation of LSF in IT population compared with HSF. Furthermore, our results showed a systematic category representation difference over SFs in fast and slow trials, while the category information was similar for unfiltered stimuli in both fast and slow trials. These observations suggest a direct link between SF processing and evolution of category information over time. Together, these results provide evidence for the existence of an effective interaction between SF coding and category representation in IT cortex.

Disclosures: **B. Karami:** None. **R. Koushki:** None. **E. Rezayat:** None. **F. Shakerian:** None. **A. Vahabie:** None. **M. A. Dehaqani:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

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Program #/Poster #: 490.18/N15

Topic: D.07. Vision

Support: NIH K99AG054732

Title: Noise correlations facilitate faster and more robust learning

Authors: *M. R. NASSAR;
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Abstract: The brain represents information in distributed population codes in which particular feature values are encoded by large numbers of neurons. A theoretical advantage of distributed population codes is that a pooled readout across many neurons can effectively reduce the consequences of stimulus-independent variability (noise) in the firing of individual neurons. However, the degree to which this benefit can be employed in practice is limited by noise correlations, or the degree to which stimulus-independent variability is shared, particularly across the subset of neurons that encode a particular stimulus feature (eg. motion direction). In particular, positive noise correlations between neurons that share the same stimulus tuning reduce the amount of decodable information in the neural population. Nonetheless, this type of

noise correlation is reliably observed, particularly between pairs of neurons that provide evidence for the same choice or perceptual categorization, raising the question of why should noise be distributed in this task- and tuning- specific manner. Here I propose that, while potentially constraining the amount of information encoded, such noise correlations reduce the dimensionality of the population response leading to faster and more robust learning. I test this idea with a neural network model of a two alternative forced choice perceptual discrimination task, in which the correlation among similarly tuned neurons can be manipulated independently of the overall population signal to noise ratio. Higher noise correlations led to faster learning of optimal readout and reduced sensitivity to adversarial noise profiles. These results suggest that noise correlations may serve to reduce the dimensionality of learning thereby making it more rapid and robust.

Disclosures: M.R. Nassar: None.

Poster

490. Visual Learning, Memory, and Categorization

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: D.07. Vision

Support: NIH Grant R01- EY025018

Title: Altered excitatory and suppressive contributions to binocular contrast interactions in visual cortex in amblyopia

Authors: *C. HOU, S. NICHOLAS, P. VERGHESE;
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Abstract: Binocular interactions in strabismic amblyopia are typically reported as being absent or greatly reduced due to preferential loss of excitatory inputs from the nonfixating eye (Sengpiel and Blakemore, 1994). Here we studied the neural dynamics of binocular interactions at various visual cortical areas in human amblyopic and normal-vision observers, using source-imaged Steady State Visual Evoked Potentials (SSVEP) over a wide range of relative contrast between the two eyes. A pair of parallel grating stimuli, one in each eye, modulated at distinct temporal frequencies allowed us to quantify spectral components associated with the individual stimuli from each eye (self-terms) and responses due to nonlinear interaction between the inputs from the two eyes (IM terms). Fitting both self and IM terms across different cortical areas simultaneously to a family of divisive gain control models (Tsai et al., 2012) indicated that both forms of binocular interaction shared a common gain control nonlinearity. However, our model fits revealed different contributions from excitatory and suppressive activities across the visual cortical hierarchy in both anisometropic and strabismic amblyopia, compared to normal-vision

observers. Strabismic amblyopes showed extraordinarily strong suppressive activities (high suppressive/excitatory ratio) across various areas including V1, V3a, hV4 and lateral occipital cortex, except for hMT+, compared to normal-vision observers. Anisometropic amblyopes showed a similar pattern of suppressive/excitatory ratio across visual areas, except for hV4, to normal observers. Our findings suggest that in addition to the loss of excitatory inputs from the strabismic eye, suppression in the visual cortex also plays an important role in loss of binocular interactions in strabismic amblyopia.

Disclosures: C. Hou: None. **S. Nicholas:** None. **P. Verghese:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.20/N17

Topic: D.07. Vision

Title: Quantifying transfer learning in mice across change detection tasks

Authors: *I. MAGRANS DE ABRIL, D. OLLERENSHAW, M. GARRETT, S. R. OLSEN, P. A. GROBLEWSKI, S. MIHALAS;
Allen Inst. for Brain Sci., Seattle, WA

Abstract: Transfer learning can be described as the ability to apply past learning to influence current and future learning. Different degrees of transfer learning can be observed in all animals: It has been shown rodents trained to identify a triangle drawn with a solid line are unable to identify as the same object another triangle drawn with dots, while chimpanzees and humans can do so [Haskell, R. E. Elsevier 2000]. On the other hand, mice are found to be a suitable model to study transfer learning using auditory discrimination experiments [Kurt, S., & Ehret, G. PNAS 2010] or active to passive avoidance [Sprott, R. L., & Stavnes, K. L. Animal Learning & Behavior 1974].
We use data from the Allen Brain Obsevatory – Visual Behavior, standardized *in vivo* survey of physiological activity in the mouse visual cortex while performing a change point detection task. Mice are presented a sequence of images (initial training on gratings with a later transition to grayscale natural images) each for 250 ms. In later training stages, mice are shown a gray scale screen for 500 ms between each image. Animals are trained to respond when the current image is different from the previous image in a go/no-go modality.
Here, we systematically quantify the transfer learning capacity and the speed of transfer in 24 mice at different stages of a visual behavior task. We compare a running d prime for a window of 20 trials between the last session of the previous training phase and the first session of new phase.
The initial change detection training phase took on average 2 days with an average of 300

trials/day. We found the transfer between different stages has distinct time scales as a function of the complexity of the change. A near transfer learning experiment consists of changing the set of natural images presented to the mice. In average, mice adapted within 10 trials. An intermediate TL experiment consists of change from gratings to natural images. In this experiment, mice adapted to an increasing representation complexity (from 2 types of gratings to 8 distinct natural images) in about 40 trials. Finally, we ran a far transfer which consisted of adding 500 ms "grey screen" flashes between every natural image, thus changing the environment dynamics. In average, mice adapted to this experiment in about 100 trials.
This study suggests a fast transfer of learning when compared to initial learning, but multiple time scales for different types of transfer complexities.

Disclosures: I. Magrans De Abril: None. **D. Ollerenshaw:** None. **M. Garrett:** None. **S.R. Olsen:** None. **P.A. Groblewski:** None. **S. Mihalas:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.21/N18

Topic: D.07. Vision

Title: Uncovering the mechanisms of short-term memory in a visual change detection task

Authors: *B. HU, J. SHANG, M. GARRETT, M. T. VALLEY, P. A. GROBLEWSKI, D. R. OLLERENSHAW, J. WATERS, C. KOCH, S. R. OLSEN, S. MIHALAS;
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Abstract: The maintenance of short-term memories is critical for survival in a dynamically changing world. However, the exact form of short-term memory used in neural circuits is unclear. Previous experimental and modeling studies suggest that this memory could either be stored in the form of persistent neural activity or synaptic efficacies via short-term plasticity. Here, we test these two hypotheses in the context of a visual change detection task. Mice were trained to respond to changes in a sequence of natural images while neural activity was recorded using two-photon calcium imaging. We also trained two different models to perform the same visual change detection task. Compared to a recurrent neural network, we find that a feedforward neural network with short-term synaptic depression better captures the asymmetry in responses to image changes in mice and is consistent with the observed adaptation in neural responses across repeated stimuli. Our model also generalizes to novel image sets that it was not trained on, similar to the behavior of mice. A set of optogenetic experiments show that silencing neural activity during an image change impairs behavioral performance, while silencing neural activity prior to the change has no effect. These findings suggest that memory maintenance occurs outside of the visual system, which is consistent with our model as short-term depression is only

incorporated in layers after the encoding of the stimulus. Our results suggest that short-term synaptic depression may serve as an important bottom-up memory signal that can be used by downstream decision-making areas.

Disclosures: **B. Hu:** None. **J. Shang:** None. **M. Garrett:** None. **M.T. Valley:** None. **P.A. Groblewski:** None. **D.R. Ollerenshaw:** None. **J. Waters:** None. **C. Koch:** None. **S.R. Olsen:** None. **S. Mihalas:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.22/N19

Topic: D.07. Vision

Support: ERC Grant

Title: Investigating the neural embodiment of prosthetic limbs and tools

Authors: ***H. R. SCHONE**[1,2], R. O. MAIMON MOR[3], C. I. BAKER[1], T. R. MAKIN[2];
[1]Lab. Brain and Cognition, NIH, Bethesda, MD; [2]Inst. of Cognitive Neurosci., Univ. Col. London, London, United Kingdom; [3]Nuffield Dept. of Clin. Neurosciences, Univ. of Oxford, Oxford, United Kingdom

Abstract: Advancements in robotics and information technology have led to the development of highly innovative artificial prosthetic limbs. Despite these advancements, low rates of prosthetic hand usage and even complete device rejection are commonplace amongst amputee populations (Cordella et al. 2016). While significant efforts are being taken to develop technological solutions to combat these issues, little attention is given to potential neurocognitive bottlenecks, such as embodiment (Makin et al. 2017). Recent evidence from our lab has shown that the more amputees use a prosthetic hand, the more the prosthesis is represented as a hand (body-part) (van den Heiligenberg et al. 2018). Thus, amputees that use a prosthesis the most (e.g. in the most hand-like way) should have the greatest propensity to successfully embody the prosthesis. Therefore, we designed a study to investigate the neural representation of prosthetic hands in individuals with the most successful prosthesis usage (e.g. elite prosthesis users, n=4) to determine if a prosthetic hand is represented as either an expert tool or a hand substitute. We included two control groups: able-bodied expert tool users (litter-pickers, n=7) and able-bodied novices (n=15). Using fMRI, we evaluated the representational structure of hands, tools and prostheses, across the body-representation and tool-use networks. To activate these representations, we presented first-person perspective videos depicting actions performed by either a hand, a prosthesis, a litter-picker or an unknown tool. Additionally, using a large battery of behavioural tasks, we investigated other neurocognitive characteristics (e.g. intrinsic

motivation, cognitive load, motor skill) that could promote successful prosthesis/tool usage. Overall, our results help to elucidate the brain's ability to represent and control an artificial device as a body part.

Disclosures: H.R. Schone: None. **R.O. Maimon Mor:** None. **C.I. Baker:** None. **T.R. Makin:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

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Program #/Poster #: 490.23/N20

Topic: H.02. Human Cognition and Behavior

Support: Arrowsmith School

Title: A brief intensive learning intervention affects resting state connectivity and neuropsychological test performance

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Abstract: Cognitive training can result in complex changes in behavior and potentially beneficial outcomes for many psychological and neurological conditions (e.g., age-related cognitive decline, traumatic brain injury, learning disability). However, at a neurobiological level, the alterations caused by particular training regimens remain largely unexplored. Further, whether the benefits of cognitive exercises are limited to domains specific to the exercises or have broader effects is currently a subject of debate. We have begun to explore these issues by evaluating the effects of a period of intensive training in a single task on the functional connectivity of four resting-state networks and a limited set of cognitive tests from the Woodcock-Johnson IV battery.
The subjects were 29 students, age range 11-19 years, enrolled in the Cognitive Intensive Program at the Arrowsmith School in Toronto, Ontario, Canada. Students practiced the Symbol Relations Task (a computer-based sustained visual-spatial attention task of progressively increasing difficulty) for five hours per day, five days per week, for six weeks. At the beginning and end of the program the students were given a subset of Woodcock-Johnson IV Cognitive tests (Letter Pattern Matching, Numbers Reversed and Pair Cancellation; used to calculate Cognitive Processing Speed and Cognitive Efficiency) and resting-state fMRI images were collected using a Siemens 3T scanner. The CONN toolbox was used to assess changes in four resting-state networks (Default Mode, Dorsal Attention, Salience, and Frontoparietal Control). Students showed variable degrees of improvement in their Symbol Relations performance over

the training period. The connectivity between the Default Mode network and the other three networks displayed significant increases that were proportional to the improvement. The strongest and most common connectivity changes were between regions of the Default Mode and Salience networks. Scores in the Woodcock-Johnson assessments significantly improved except for Numbers Reversed, a measure of short-term working memory. Overall, this study demonstrates that training in the Symbol Relations task strengthens resting-state functional connectivity that may underlie improved cognitive performance.

Disclosures: G.M. Rose: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Arrowsmith School. **A.C. Jagger-Rickels:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.24/N21

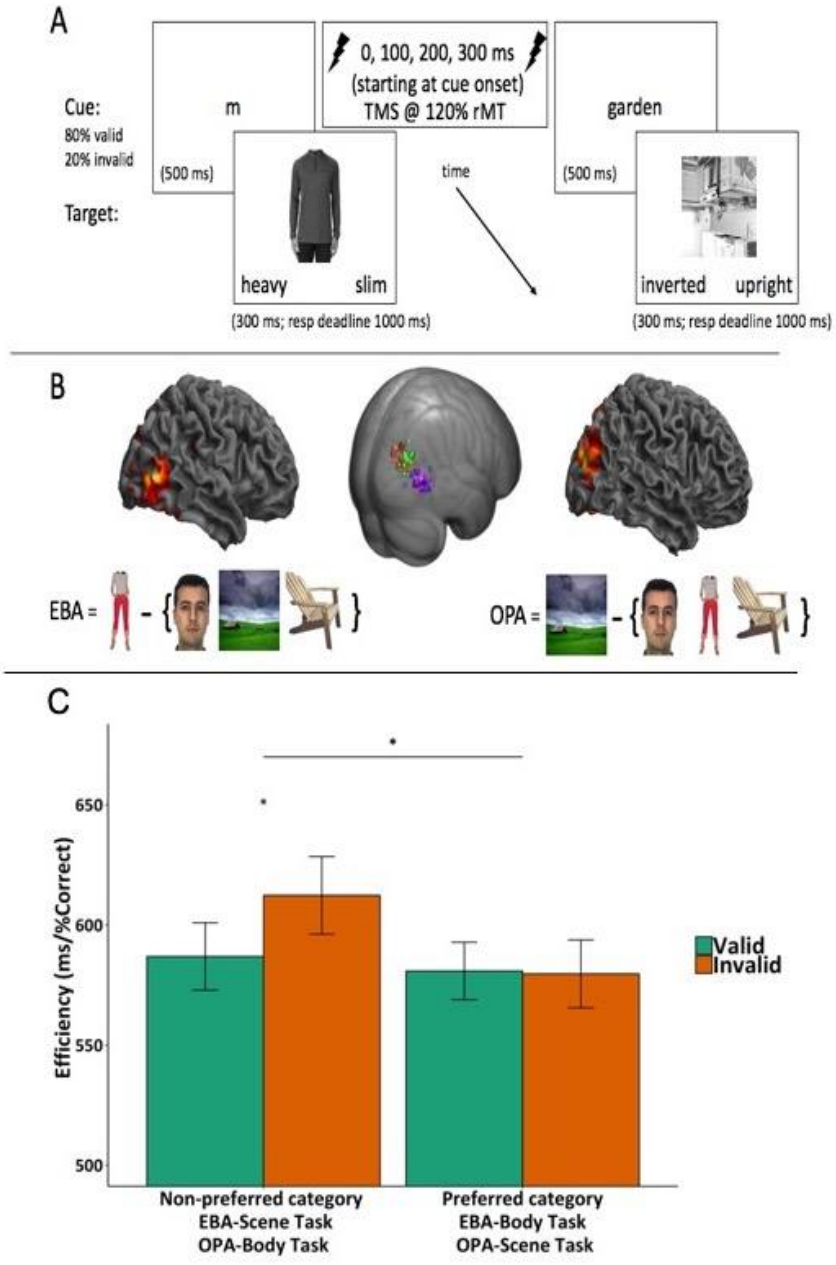
Topic: D.07. Vision

Title: Causal evidence for expression of perceptual expectations in category-selective extrastriate regions

Authors: M. GANDOLFO, *P. E. DOWNING;
Sch. of Psychology, Bangor Univ., Bangor, United Kingdom

Abstract: Expectations about a visual event strongly shape the way it is perceived**.** Valid cues that predict a target's content or location can improve its detection and discrimination over a range of perceptual tasks. A candidate brain mechanism that supports these cue-driven expectations consists in the prior activation of neural populations that represent the target. Here we provide causal evidence that cue-driven activity in extrastriate category-selective brain regions is directly involved in forming perceptual expectations about the content of a visual target. We tested two visual tasks that demonstrate the effects of verbal cues on the efficiency of perceptual judgments. In a body perception task, valid verbal pre-cues about the sex of a target body image ("m" or "f") improved performance (compared to invalid cues) on binary judgments about the weight of the depicted person. Analogously, in a scene perception task, valid verbal cues about the semantic category of a scene ("kitchen" or "garden") improved performance (compared to invalid cues) on judgments of the target image's orientation, which was either upright or inverted (Fig. 1A). In two further experiments (N=21 each) we used fMRI-guided online transcranial magnetic stimulation (TMS, Fig. 1B) to demonstrate that cue-driven neural activity in category-selective occipitotemporal regions is causally necessary for cueing effects to be expressed in these tasks. TMS was delivered online in each trial, starting at cue onset (4 pulses, 10 Hz) and ending 200 ms before target onset. In the body perception task, TMS delivered over EBA (extrastriate body area) but not over OPA (occipital place area) eliminated

the validity effects of the cues. Likewise, in the scene perception task, stimulation over OPA but not over EBA eliminated the validity effects of the verbal cues (Fig. 1C). In a site and task specific manner, we have established causal evidence that cue-driven brain activity in occipitotemporal category-selective areas, arising before the appearance of a target image, is critical for the expression of perceptual expectations.



Disclosures: **M. Gandolfo:** None. **P.E. Downing:** None.

Poster

490. Visual Learning, Memory, and Categorization

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 490.25/N22

Topic: D.07. Vision

Support: NSF Grant PHY-1532846
Mohapatra Fellowship in Vision Research
Leon Levy Fellowship

Title: Functional changes in areas V1 and V4 during the course of perceptual learning

Authors: *G. L. ASTORGA[1], M. CHEN[1], Y. YAN[2], W. LI[2], C. D. GILBERT[1];
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Abstract: We have previously shown that neurons in visual areas V4 and V1 are adaptive processors, differentially responding to the identical set of stimulus attributes in a task-dependent manner. Neuronal activity is strongly modulated by task-relevant attributes and weakly modulated by irrelevant ones, reflecting top-down influences of expectation and perceptual task. In the current study we took a step further to investigate whether this top-down modulatory mechanism could be modified over the course of perceptual learning. For a monkey previously trained on bisection and vernier discrimination using a set of five-line stimuli, we implanted microelectrode arrays in areas V4 and V1 at locations representing an untrained part of the visual field. The animal was cued to discriminate the positions of the central line in the five-line stimuli, either relative to two parallel flanking lines (the bisection task) or relative to two collinear lines (the vernier task). The animal's discrimination thresholds decreased with training in both tasks. Remarkably, at the early training stages few neurons in V1 but many neurons in V4 showed differential tuning properties between the two tasks performed on the same set of stimuli. After weeks of training, however, most neurons in both areas showed the task dependency. Once present in V1, the manifestation of task-dependent information in V1 precedes that in V4 by 45msec within any given trial. These results suggest a progressive shift of task-dependent top-down influences from higher-tier areas to earlier stages in the cortical hierarchy as animals become proficient in the task.

Disclosures: G.L. Astorga: None. **M. Chen:** None. **Y. Yan:** None. **W. Li:** None. **C.D. Gilbert:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.01/N23

Topic: D.08. Visual Sensory-motor Processing

Support: NSERC Discovery Grant
NSERC CGSM
University of Manitoba Psychology Graduate Fellowship

Title: Grasping in a cluttered environment: Avoiding obstacles under memory guidance

Authors: *H. H. ABBAS, J. J. MAROTTA;
Psychology, Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: We often reach for remembered objects, such as when picking up a coffee cup from behind our morning paper. In cases like this, we rely on visuospatial memory, encoded by the perceptual mechanisms of the ventral visual stream, to guide our actions, rather than on the real-time control of action by the dorsal visual stream (Milner & Goodale, 1995). Further, our motor plans must often accommodate for the messy spaces within which we act, avoiding irrelevant objects in our way. Little research has examined memory-guided grasping during instances of obstacle avoidance, though it is likely that obstacles perceived by the ventral stream as more threatening will produce exacerbated avoidance strategies. This study examined how the availability of visual feedback altered eye-hand coordination in an obstacle avoidance paradigm. Eye and hand movements were monitored as subjects had to reach through a pair of obstacles in order to grasp a 3D target object, under full visual feedback (visually-guided; n = 12), immediately in the absence of visual feedback (memory-guided no-delay; n = 12), or after a 2-s delay in the absence of visual feedback (memory-guided delay; n = 12). The positions and widths of obstacles were manipulated, though their inner edges remained a constant distance apart. We expected the memory-guided delay group to exhibit exaggerated avoidance strategies due to a reliance on the perceptual mechanisms of the ventral steam. Results revealed successful obstacle avoidance and grasps of the target object in all groups, however different avoidance strategies emerged depending on the availability of visual information. The visually-guided and memory-guided no-delay groups used real-time visual information to alter the paths of the index finger and wrist and adjust final index finger positions on the target object, to account for obstacles differentially obstructing the reach path. Still, the no-delay group showed wider index finger paths and a failure to adjust final fixations, resulting from the inability to use visual information for the online control of action. Contrary to expectation, the memory-guided delay group employed a more moderate strategy for avoiding obstacles, with fewer instances of altered index finger and wrist paths or adjusted index finger positions on the target object in response to

positioned obstacles. It seems in the absence of real-time visual information, reaches to remembered objects even after a brief delay follow a “good enough” approach for avoiding obstacles. To conclude, under the perceptual control of the ventral stream, obstacle avoidance behaviour adopts a more moderate, rather than exaggerative, strategy.

Disclosures: H.H. Abbas: None. **J.J. Marotta:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.02/N24

Topic: D.08. Visual Sensory-motor Processing

Support: Supported by the Canada First Research Excellence Fund

Title: Head motion optimizes binocular vision during head-unrestrained reaches

Authors: *H. AL-TAHAN[1,2,3,4,5], J. CRAWFORD[1,2,3,4];
[2]Ctr. for Vision Res., [3]Vision: Sci. to Applications, [4]Departments of Psychology, [5]Dept. of Electrical Engin. and Computer Sci., [1]York Univ., Toronto, ON, Canada

Abstract: Experiments in both monkeys (Arora et al., 2017) and humans (Al-Tahan & Crawford, 2018) have shown that head motion is prolonged and increased when gaze shifts are accompanied by reaches to the same target. This faces the head more toward the target and increase drive to the VOR, resulting in the eyes being more centered in the head during reach. Here, we tested the hypothesis that this motor strategy optimizes depth vision for reach. Specifically, we tested if removing binocular vision reduces reach-related head motion. As in our previous experiment, right eye / hand dominant participants (n=15) were instructed to perform gaze shifts (with or without reach movements) toward visual targets on a 40° x 20° computer screen array placed 60 cm forward from the eye. However, on half of the trials, we masked the non-dominant eye to remove binocular vision. Right eye and hand movements were measured using an *EyeLink II* eye tracker and two *Optotrak* cameras respectively. Preliminary analysis replicated our previous results, i.e., compared to no-reach controls (in the non-masked condition), reach movements were accompanied by larger (M = 3.14º, SD = 1.01º; P =) and faster (M = 8.71º/s, SD = 2.40º/s; P =) head motion, as well as more accurate gaze shifts toward the target (M = 1.92º, SD = 0.42º, P =). However, when the non-dominant eye was masked, head motion was significantly reduced during reaches (M = 2.02º, 0.56º, P = 0.013), but not in the no-reach control task (M = 0.34º, SD = 0.02º; M = 0.30, SD = 0.04º; P = 0.30). Furthermore, head movements were significantly slower (P = 0.048) when the non-dominant eye was masked during reaches (M = 9.21º/s, SD = 1.44º/s; M = 7.34º/s, SD = 1.32º/s), but not in the no-reach control task. Final gaze position showed significantly lower errors when the non-dominant eye

was masked in both reach (M = 1.92º, SD = 0.42º; M = 3.42º, SD = 0.23º; P < 0.001) and control tasks (M = 2.69º, SD = 0.39º; M = 4.51º, SD = 0.27º; P < 0.001) task. These results show that both reaching and binocular vision influence eye-head gaze kinematics and are consistent with the notion that head motion supports binocular vision to optimize accurate reaching in depth.
Arora, H. K., Bharmauria, V., Yan, X., Wang, H., Sun, S., and Crawford, J. D. (2017) Coordination of eye, head and hand movements during visually guided reaching in head unrestrained Rhesus monkeys. Society for Neuroscience Conference, San Diego, CA, USA. Program No. 495.04/GG3.
Al-Tahan, H. and Crawford, J. D. (2018) To reach or not to reach: Coordination of eye, head and hand movements during visually guided reach. Society for Neuroscience Conference, San Diego, CA, USA. Program No. 399.23/LL6.

Disclosures: H. Al-Tahan: None. **J. Crawford:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.03/N25

Topic: D.08. Visual Sensory-motor Processing

Title: Effects of initial arm posture on reach endpoint variability

Authors: *P. K. PHATARAPHRUK[1], Q. RAHMAN[3], M. FRUCHTMAN[4], K. LAKSHMINARAYAN[5], C. A. BUNEO[2];
[1]Sch. of Biol. and Hlth. Systems Engin., [2]Arizona State Univ., Tempe, AZ; [3]Univ. of Arizona Col. of Med., Phoenix, AZ; [4]Univ. of Michigan, Ann Arbor, MI; [5]Cleveland Clin. Fndn., Cleveland, OH

Abstract: Reaching movements are corrupted by neural noise that occurs during the planning and execution stages of movement production, contributing to reaching variability (RV). Previous work has shown that when visual feedback is present, RV is dominated by noise associated with arm and target position estimation in visual coordinates. In the absence of vision, variability is more influenced by movement direction, suggesting a stronger role for execution-related noise in muscle coordinates. Based on these findings we hypothesized that RV would depend not only on movement direction but also on initial arm configuration, particularly without vision. This hypothesis was tested using a memory-guided reaching movement task. Human subjects (N=10) performed reaching movements to three virtual frontal plane targets using either adducted or abducted initial right arm postures. On alternate trials, vision of the hand was either continuously present or removed on movement onset. Analysis focused on differences in reach endpoint distributions, which were parametrized by their volume, aspect ratio (distribution shape), and orientation in 3D space. Differences in volume and aspect ratio were

analyzed using a two-way repeated measures ANOVA (factors: visual condition and target location). For orientation a two-way circular ANOVA was used. An alpha of 0.05 was applied for all tests. Results showed endpoint distribution volumes were generally smaller and less variable across subjects when hand vision was available, while aspect ratios tended to be similar for the two visual conditions. For both volume and aspect ratio, little variation with target location was observed. Orientations varied systematically with target location in the vision condition but were highly variable and showed no consistent trends with location when vision was withheld. Regarding the influence of initial arm posture, differences in volume and orientation between postures were found to be larger when vision of the moving hand was withheld. Differences in aspect ratio showed no dependence on the visual conditions and no distribution parameter showed a dependence on target location. In summary, changes in endpoint variability between arm postures were apparent in this study and were larger when visual feedback was absent. This suggests that when vision of the moving hand is removed, endpoint variability is determined largely by execution noise in muscle coordinates.

Disclosures: P.K. Phataraphruk: None. **Q. Rahman:** None. **M. Fruchtman:** None. **K. Lakshminarayan:** None. **C.A. Buneo:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.04/N26

Topic: D.08. Visual Sensory-motor Processing

Support: NICHD R01 HD090125
NINDS R01 NS065065

Title: Brain-computer interface decoding during a sensory-critical task

Authors: *S. SEKHAR[1], E. R. OBY[1], N. T. MCCLAIN[1], A. P. BATISTA[2], P. J. LOUGHLIN[1]; [2]Bioengineering, [1]Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Traditionally, brain-computer interface (BCI) tasks have focused on decoding movement intent during simple goal-directed movements such as center-out reaches. However, in real-world contexts, most of the movements we make require constant sensory feedback. Decoding movement intent in these contexts may provide a challenge in part due to the constantly changing sensory feedback. To help create BCI decoders that can work in realistic behavioral contexts, we adapted the Critical Stability Task (CST) from the human performance literature (Jex et al., 1966). The CST is a prolonged motor control task for which sensory feedback is crucial, wherein subjects interact with an inherently unstable virtual system and must generate continuous sensory-guided actions to balance it at an equilibrium point. The CST

provides a platform where we can design BCI decoders that might provide rich control for feedback-guided movements that are typically sudden and very precise. As a first step toward a real-time BCI algorithm that can execute the CST well, we performed offline BCI reconstructions of hand movements during the CST paradigm. We recorded from motor cortex of two Rhesus monkeys using multielectrode Blackrock arrays. The monkeys performed the CST with their hands, and we reconstructed kinematics from neural activity using BCI decode algorithms. Our accuracy in reconstructing hand kinematics from neural activity was overall quite high, which holds promise for future real-time BCI decoding in the CST paradigm. Additionally, this reassuring outcome provides a testbed for further offline explorations. In particular, we will examine: (1) Can we reconstruct cursor motion as accurately as hand movement from M1? This is possible to ask in the CST, since the two are more dissociated than they are in standard center-out paradigms. (2) Does BCI calibration generalize? That is, if we calibrate a decoder using CST, does it also function well in a center-out paradigm? (3) Do different families of BCI decode algorithm (Kalman filter vs optimal linear estimator, for example) do better at decoding different aspects of the kinematics. (4) Does decode performance change with task difficulty or as sensory feedback becomes more critical for performance?

Disclosures: S. Sekhar: None. **E.R. Oby:** None. **N.T. McClain:** None. **A.P. Batista:** None. **P.J. Loughlin:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.05/N27

Topic: D.08. Visual Sensory-motor Processing

Support: Canadian Institutes of Health Research (CIHR)
Vision: Science to Applications (VISTA) scholarship by Canada First Research Excellence Fund

Title: Hand orientation is influenced by gaze location and saccades in a visual memory-guided alignment task

Authors: *G. N. LUABEYA[1,2,3,4], X. YAN[1,2,3], J. D. CRAWFORD[1,2,3,4,5];
[2]Ctr. for Vision Res., [3]Vision Sci. to Applications (VISTA), [4]Biol., [5]Psychology, [1]York Univ., Toronto, ON, Canada

Abstract: Although visually-guided grasps have been studied extensively, the influence of gaze direction on hand alignment to a seen or remembered object is unclear. Our study uses a memory-guided alignment task to investigate the influence of gaze position and saccades on hand location and orientation. For Experiment 1 (gaze position), participants reached and aligned

an object to a rectangular outline presented on a computer screen in three possible orientations: 0º (horizontal), +45º and -45º. Gaze fixation was central or to the left/right. The target outline was either presented briefly in complete darkness (memory task) or remained illuminated along with visual feedback of the hand (visual task). Comparing the memory task to the visual task, there was a significant main effect of gaze location: participants aimed further to the right of the target when fixating to the left (a 'gaze-dependent overshoot'). There was also an interaction between gaze location and orientation: when looking to the right, participants over-rotated (too CCW for -45º and too CW for +45º), whereas when they looked to the left, they under-rotated (too CW for -45º and too CCW for +45º). There were significant interactions between task, orientation, and gaze position for variable errors. As expected, location was more precise in the visual task, and during central gaze fixation. Likewise, orientation was more precise in the visual task. Fixating a remembered target provided less advantage for orienting precision than for location. Since the difference in orientation was mainly seen in the +45º and -45º orientations, Experiment 2 (saccades) required participants to reach and align the object to either a +45º or a -45º rectangular target. They performed two types of saccades (from central fixation to the left/right gaze fixations or between the peripheral left/right fixation points) during the memory interval. Preliminary results suggest that saccades between the peripheral fixation points produce the classic 'overshoot updating' effect (Henriques et al. J. Neurosci. 1998), but also introduces systematic and variable errors in orientation. Overall, our location results confirm the gaze-dependencies observed in pointing studies, whereas our orientation results reveal several additional interactions between vision, memory, gaze position, and saccades during memory-guided manual alignment.

Disclosures: G.N. Luabeya: None. **X. Yan:** None. **J.D. Crawford:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.06/N28

Topic: D.08. Visual Sensory-motor Processing

Support: KAKENHI JP16H06566

Title: Synthetic modeling of human visual motion analysis for generating quick ocular and manual responses

Authors: *H. GOMI, D. NAKAMURA;
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Abstract: Human visual motion analysis has crucial roles for quickly adjusting posture, eyes, and limbs in dynamic interaction with environments. It has been revealed that both of ocular and

manual following responses (OFR and MFR) induced by a suddenly applied visual motion are highly sensitive for the visual motion of low-spatial and high-temporal frequency stimulus (under 0.1 cpd and over 10 Hz) [Gomi et al. 2006], whereas those specificities are greatly different from the perceptual sensitivity to visual motion. In addition, OFR and MFR are modulated differently depending on the size and location of visual motion with various spatiotemporal frequencies [Gomi et al. 2013].
Here we examined as to whether these OFR and MFR specificities are acquired by the statistical relationship between the visual motion and self-motion, based on the hypothesis that the function of these rapid responses is to reduce the error (i.e., retinal slip for OFR and reaching error for MFR) caused by self-motion. First, we trained a convolutional network to estimate translational velocities and angular velocities of self-motion from image sequences. The images and self-motion data were recorded by a head-mounted camera during several kinds of daily human movements. High correlation coefficients between the actual and estimated self-motion for the test dataset after learning ($r > 0.8$ for 6-DoF) indicate a successful estimation of self-motion from the time-sequential images although complex computation is required to estimate self-motion from images in the conventional geometry. Interestingly, high estimation performance was preserved for the low-pass (< 0.1 cpd) filtered images while performance was degraded for the high-pass (> 0.4 cpd) filtered images, suggesting that self-motion was dominantly estimated from the low-spatial frequency components. This feature is analogous to the high sensitivity features of OFR and MFR for low spatial frequency stimulus. Additionally, we found some degree of similarity between stimulus-area dependent modulations of the angular component of the modeled network and of OFR and between stimulus-area dependent modulations of the translational component and of MFR. These results would be consistent to the findings in previous experiments that the area MST encodes a self-motion and contributes to generate OFR and MFR, and therefore support the hypothesis that these implicit motor responses have a function to reduce the corresponding errors caused by self-motion.

Disclosures: H. Gomi: None. **D. Nakamura:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.07/N29

Topic: D.08. Visual Sensory-motor Processing

Title: Enhanced visual detection and visuomotor control in somatosensorily-impaired individuals

Authors: *F. R. SARLEGNA[1], A. RENAULT[2], F. MATONTI[3], J. COLE[4], R. C. MIALL[5]; [1]CNRS and Aix-Marseille Univ., Marseille, France; [2]Aix-Marseille Univ. & CNRS, Marseille,

France; [3]INT, Marseille, France; [4]Poole Hosp., Poole, United Kingdom; [5]Sch. of Psychology, Univ. of Birmingham, Birmingham, United Kingdom

Abstract: Previous research has shown that blind individuals have supranormal abilities in tactile discrimination (van Boven et al. 2000), which is presumably linked to the fact that cortical reorganization in blind leads to the so-called visual cortex to process tactile information (Sadato et al. 1996; Cohen et al. 1997). What would happen to individuals devoid of tactile and proprioceptive information? There is ample evidence that cross-modal plasticity can result in enhanced perceptual abilities in impaired individuals compared to healthy subjects. This idea stems for instance from studies on blind but also deaf individuals, who can have enhanced visual abilities (Bavelier et al. 2006; Lomber et al. 2010). Here we tested the visual perception of two patients with massive yet specific loss of touch and proprioception, using the classic clinical Goldmann's test of kinetic visual field. We found that the visual field is larger in the two chronically deafferented subjects GL (Sarlegna et al. 2010) and IW (Miall and Cole 2007) compared to age-matched controls. More specifically, their detection of visual stimuli was enhanced only in far peripheral vision (>70°), both in monocular and binocular conditions. The superior visual performance may reflect a functional correlate of plasticity of the somatosensory cortices and extend the view of cross-modal plasticity to subjects who suffered acquired deafferentation. To study the impact of the somatosensory loss and the enhanced visual detection on visuomotor function, a prism-adaptation paradigm was tested on healthy-control participants and the two deafferented participants. Results showed that in contrast to controls who were perturbed by the prisms, both deafferented participants rapidly adapted their reaching behavior to the prisms. These findings indicate that visuomotor adaptation is not necessarily driven by a visuo-proprioceptive mismatch. While deafferented participants may be experts at processing of visual information (Blouin et al. 1993; Ghez et al. 1995; Lefumat et al. 2016), our results suggest that visuomotor adaptation is primarily driven by a mismatch between the predicted outcome of the motor commands and visual feedback.

Disclosures: F.R. Sarlegna: None. **A. Renault:** None. **F. Matonti:** None. **J. Cole:** None. **R.C. Miall:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.08/N30

Topic: D.08. Visual Sensory-motor Processing

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NIH Grant 1S10 RR-12873

Whitehall Foundation
Charles and Johanna Busch Faculty Research Grant
Mind Science Foundation
National Partnership for Advanced Computational Infrastructure

Title: Invariant read-out of eye position from population codes with high-dimensional selectivity

Authors: *J. R. MCFADYEN[1], B. HEIDER[2], A. N. KARKHANIS[2], S. L. CLOHERTY[1], F. A. MUÑOZ[2], R. M. SIEGEL[2], A. P. MORRIS[1];
[1]Monash Univ., Melbourne, Australia; [2]Rutgers Univ., Newark, NJ

Abstract: Neural activity encodes information about our intentions and cognitions, and about the external world. In posterior parietal cortex (PPC), for example, single neurons encode the locations of objects, motor plans to reach toward them, and the current posture of the eyes, arms, and body - and often with inseparable joint tuning. A challenge for downstream computation is thus to extract relevant signals from the population activity while ignoring the influence of irrelevant ('nuisance') variables. Here we show that a key spatial variable for vision, gaze direction, can be decoded accurately from population activity in PPC even though the gaze direction tuning of individual neurons changed across sensory and behavioral contexts. We measured extracellular spiking during different stages ('contexts') of a visually-guided reaching task, including a fixation epoch with minimal visual stimulation, a visually-rich delay epoch in which a reach was planned, a "go" epoch, and during the reach. Fixation was maintained throughout the trial at one of nine locations. We found that a decoder trained on activity in the delay context provided accurate estimates of eye position across all other contexts, largely overcoming the non-stationary tuning of single neurons. Where biases did arise, they were substantially improved by a modified decoder that accounted for global differences in responsivity of neurons across contexts. These results reveal a surprisingly invariant population code for eye position that is available via a fixed (i.e. naïve) read-out. Using simulations, we show that such invariance is expected provided that context effects operate along dimensions of the population response that are orthogonal to that of the target latent variable. Our study suggests an efficient strategy for structuring information in multiplexed population codes so that it is selectable for perception (e.g. attention), cognition (e.g. decision variables), and motor control (e.g. action targets) regardless of context.

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Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.09/N31

Topic: E.04. Voluntary Movements

Title: Prehensile synergies are robust to expectations of rapid upcoming movement changes

Authors: *A. S. NAIK, A. KULKARNI, S. AMBIKE;
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Abstract: Stability is the ability of the motor system to maintain a motor state by rejecting disturbances. Stability of the forces produced by the fingers in an isometric pressing task is reduced prior to self-initiated force changes and when a change in the force is expected, independent of whether the change is executed. Here we explore if similar anticipatory stability changes occur in response to the mere expectation of movement change in an object manipulation task. During the vertical oscillation of an object, the difference in the forces of the thumb and the four fingers combined normal to the oscillation direction (i.e., along the horizontal) are stabilized around zero to minimize unbalanced forces along the horizontal direction. In contrast, non-vertical object movement requires that the normal forces are unbalanced so that the object accelerates along the horizontal direction. Therefore, we hypothesize that the stability of the normal force difference during the vertical oscillation will weaken if the participant expects to change the oscillation direction. Ten healthy participants (24.1 ± 3.9 yrs) performed oscillatory arm movements while holding an object with their digit tips. The amplitude was one-fourth their arm length, and the frequency was 3 Hz. The movement directions were vertical; horizontal (H); top left to bottom right (D1); and top right to bottom left (D2). Participants performed trials with only vertical oscillations and reaction-time trials in which initial vertical oscillations were followed by a change in oscillation direction at a random time in response to an audio-visual cue. Across conditions, the altered direction belonged to the set {H}, {H, D1}, or {H, D1, D2}. A motion capture system measured the object height, and force sensors mounted on the object measured digit tip forces. The forces for the initial vertical oscillation phase for all trials were isolated. The normal force exerted by the thumb and the sum of the normal forces of the four fingers were computed. The forces were time-normalized after aligning the peaks in the object height across multiple oscillation cycles within each experimental condition. The variance across multiple cycles in the thumb and finger normal forces yielded the stability of the normal force difference via the uncontrolled manifold analysis. We found no difference in stability across tasks ($F(4,45) = 0.18$; $p = 0.9$). Therefore, the synergy between the thumb and finger normal forces is robust to expectations of future object manipulation and the number of potential upcoming behaviours. It remains to be seen if these robust synergies influence the efficacy of alterations in object manipulation patterns.

Disclosures: A.S. Naik: None. **A. Kulkarni:** None. **S. Ambike:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.10/N32

Topic: E.04. Voluntary Movements

Support: JSPS KAKENHI 16K18367
JSPS KAKENHI 18K07348

Title: Spatial extent of repetitive TMS-induced cortical plasticity in the primary motor cortex detected by resting-state fMRI

Authors: *T. OSADA[1], K. TAMURA[1], A. OGAWA[1], M. TANAKA[1], A. SUDA[1,2], Y. SHIMO[2], N. HATTORI[2], K. KAMAGATA[3], M. HORI[3], S. AOKI[3], T. SHIMIZU[4], H. ENOMOTO[5], R. HANAJIMA[4], Y. UGAWA[5], S. KONISHI[1];
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Abstract: Repetitive transcranial magnetic stimulation (rTMS) to a cortical region induces changes in cortical excitability for minutes to hours after the end of intervention. However, it has not been precisely determined to what extent the cortical plasticity prevails spatially in the cortex. Recent studies have shown that rTMS induces changes in “interhemispheric” functional connectivity, the resting-state functional connectivity between the stimulated region and the symmetrically corresponding region in the contralateral hemisphere (Watanabe et al., Hum Brain Mapp, 2014). In the present study, quadripulse stimulation (QPS), a type of rTMS, was applied to the index finger representation in the left primary motor cortex (M1) by using a figure-of-eight coil and four magnetic stimulators (Magstim). The position of the stimulation coil was constantly monitored by an online navigator (Localite). After application of QPS, resting-state functional MRI was administered with a 3-T MRI scanner and 64-channel RF head coil (Siemens Prisma; multi-band GE EPI sequence, TR = 1.0 s, TE = 30 ms, voxel size = 2 × 2 × 2 mm). After a standard preprocessing, functional connectivity was calculated. Then, the interhemispheric functional connectivity after QPS was compared with that before QPS. A cluster of connectivity changes was observed in the stimulated region in the central sulcus. The cluster was spatially restricted to the circle of 20 mm diameter, and was approximately 10 mm long in the depth direction. A localizer scan of the index finger motion confirmed that the cluster of interhemispheric connectivity changes spatially overlapped with the activation related to the index finger motion. These results indicate that the cortical plasticity in M1 induced by rTMS

was relatively restricted in space, and suggest that the interhemispheric functional connectivity can be used to visualize the cortical plasticity induced in the stimulated region.

Disclosures: **T. Osada:** None. **K. Tamura:** None. **A. Ogawa:** None. **M. Tanaka:** None. **A. Suda:** None. **Y. Shimo:** None. **N. Hattori:** None. **K. Kamagata:** None. **M. Hori:** None. **S. Aoki:** None. **T. Shimizu:** None. **H. Enomoto:** None. **R. Hanajima:** None. **Y. Ugawa:** None. **S. Konishi:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.11/N33

Topic: E.04. Voluntary Movements

Title: The stability of the current motor state is influenced by expected movement: Do cognitive events during the inter-stimulus interval of choice reaction-time tasks have a motor counterpart?

Authors: *M. A. TILLMAN[1], S. AMBIKE[2];
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Abstract: Stability of a motor state is the ability to maintain that state by rejecting disturbances. The stability of a motor state reduces prior to a volitional motor action, or when an action is expected, independent of whether it is executed. It is also known that it takes time to establish the stability of the current motor state when it is preceded by different motor patterns. Therefore, the stability of the current motor state is influenced by prior movements and expected movements. However, the relative contributions of the two sources of destabilization are unknown. Here, we quantify the contribution of each component to the stability of the current state in a finger force production task. Twenty-two participants (age 21.04 ± 0.4 yrs) produced a force with the fingertips by pressing down on sensors. They matched a visually-presented target force in four conditions, with 20 trials per condition. In the first condition the target force was invariant, with no expectation of future movement and consistent movement history. Trials in the second condition began with an invariant target which later moved in a random fashion in the vertical direction. In the invariant-target phase, the history is consistent and there is expectation of movement. Trials in the third condition began with a randomly moving target that then became stationary. In the invariant-target phase, the movement history is variable but there is no expectation of movement. The last condition had an invariant-target phase flanked by variable prior movements and expectation of movement. The targets were color-coded so that the participant knew when to expect movement. Finger force data was analyzed over a one-second window with the target invariant, three seconds after it first became stationary. RMSE was utilized to quantify the stability of performance. Higher RMSE indicates lower stability. A main effect of Condition was discovered ($F(3,21) = 14.02$; $P < 0.01$). The stability of the finger force

was greater when no movement was expected (Conditions 1 and 3) compared to when it was expected (Conditions 2 and 4), irrespective of prior movements. This indicates that the effects of prior actions on the stability of the current state die out, whereas the effects of expected motor actions persist. The invariant-target portion resembles the inter-stimulus interval (ISI) in choice reaction time (CRT) tasks utilized in the cognitive science literature. Data from CRT studies are explained based on cognitive events that occur during the ISI. Since the stability modulation we observe is accomplished via altered muscle activation, our result suggests that the cognitive events during the ISI may be accompanied by motor events.

Disclosures: M.A. Tillman: None. **S. Ambike:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.12/N34

Topic: E.04. Voluntary Movements

Title: Stimulus onset synchrony and automatic modulation of motor response induced by a visual distractor

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Abstract: To explore the mechanism of automatic motor response modulation induced by observed visual motion, we investigated the relation between SOA (stimulus onset asynchrony) and the amplitude of visuomotor congruency effect. Visuomotor congruency effect was induced by a distractor that linearly moved toward one of eight possible directions while participants responded by moving their index finger leftward or rightward based on the presented cue (choice reaction task). A number (1 or 2) was randomly presented on the screen as a response cue. The association of the number and response direction was fixed during the experiment and counter-balanced across participants. The SOA of the distractor presentation (movement onset) and the number cue presentation varied among -50, -33, -17, 0, 17, 33, and 50 ms. Note that in trials with negative SOAs (-50, -33, and -17), the number cue was presented before the onset of distractor movement. Visuomotor congruency was defined based on the directions of finger response and distractor movement, and the congruency effect was calculated by subtracting average RT of congruent trials from that of incongruent trials. The results showed that positive congruency effect was consistently significant in all SOAs, indicating that motor planning is disturbed by visual motion the onset of which is even before (-50 ms SOA) and after (+50 ms SOA) the start of the visual processing for movement planning. This finding suggests that motor planning is not a one-shot processing based on the available information at the start of the planning but one continuously adapting preceding and subsequent environmental changes.

Disclosures: **Y. Itaguchi:** None. **D. Yoshioka:** None. **M. Miyazaki:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.13/N35

Topic: E.04. Voluntary Movements

Support: NIH Grant DP2HD087955

Title: The hand synergies of simple finger and grasping movements are encoded by a common distributed low frequency cortical network

Authors: ***N. NATRAJ**[1], D. B. SILVERSMITH[2], E. F. CHANG[3], K. GANGULY[4]; [1]Neurol., Univ. of California, San Francisco, San Francisco, CA; [2]Bioengineering, Univ. of California San Francisco, San Francisco, CA; [3]Neurosurg., [4]UCSF, San Francisco, CA

Abstract: Prior research has well documented the existence of kinematic synergies, low dimensional building blocks of complex hand movements. However, the neural representation of synergies are still yet to be precisely characterized. To this end, we measured electrocorticographic (ECoG) data over parietal, premotor and sensorimotor areas from 4 patients undergoing clinical monitoring for epilepsy as they performed self-paced grasping and finger movements. The LeapMotion system was used to measure position data from all joints of the hand as the subjects performed the movements. Statistical analysis of the kinematic covariance matrix revealed that like grasp movements, even 'simple' finger movements employed a whole hand control strategy and were characterized on average by three hand synergies. To understand the neural encoding of synergies, raw electrocorticographic data were band-pass filtered, Hilbert transformed and subsequently correlated to the synergies in a multivariate fashion via canonical correlation analyses (CCA). The goal of CCA is to find latent pairs of neural maps (derived from the original ECoG data) and hand configurations (derived from the original synergy data) that in turn produce new pairs of maximally correlated "neurokinematic" synergies. Results revealed that the amplitude of low frequency oscillations (LFO, 0.5-4Hz) produced the most correlated neurokinematic synergies. The LFO neural maps uncovered by CCA encompassed a distributed network over parietal, premotor and sensorimotor regions. Notably, the distributed low frequency network was common to both individual finger as well as grasping movements, highlighting the complexity of individual finger movements. The distributed low frequency network was a robust feature of the data as it underlay both self-paced and cue-initiated movements. Interestingly, high gamma amplitudes sampled at the LFO frequencies outperformed traditional high gamma band-based analysis and were equivalent to LFOs in terms of synergy correlations. Finally, our results revealed that the angle of similarity between the original hand synergies and the neurokinematic synergies were significantly

different from zero (60 degrees on average), implying that the neural encoding of synergies involves a rotation of the synergy space. These results here shed new light on the precise spatiotemporal relationship between a common distributed low frequency cortical network and the previous observed kinematic synergies underlying both simple finger and grasping movements.

Disclosures: **N. Natraj:** None. **D.B. Silversmith:** None. **E.F. Chang:** None. **K. Ganguly:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.14/N36

Topic: E.04. Voluntary Movements

Support: VCU Grant Submission Incentive Program

Title: Feasibility of a protocol measuring force perception in young children using a play-based assessment in the natural environment

Authors: ***R. M. MOLININI**[1], L. ANDERSON[2], J. LEE[2], K. RAHIMIAN[2], S. C. DUSING[1], V. CHU[2];
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Abstract: A sensitive period in the development of proprioception occurs before four years old. A significant knowledge gap exists regarding the timeline of proprioception development during this critical time. Previous research assessed proprioception indirectly in young children through parent reports or observations. The purpose of this abstract is to describe our initial feasibility assessment of a methodology to objectively assess a young child's development of force perception using a coloring task in their natural environment.
Two typically developing children were assessed: S1 (21 months) and S2 (52 months). Custom made crayons of different material properties and diameters with different breaking strengths were administered systematically to examine the child's force perception. There were 20 possible crayons and up to 5 trials per crayon. Subjects were given the same initial crayon. If the child did not break the crayon they received a crayon with a lower breaking strength. If the child broke the crayon they received a crayon with a higher breaking strength. If the child refused to color a different color crayon with the same breaking strength was provided. Assessments were video-taped and behaviorally coded with Datavyu 1.3.7 to identify the duration of coloring. In future research, the durations of coloring before break will be plotted against the crayon breaking strength to determine force perception thresholds, or the point at which the child can regulate

their force to prevent breakage. Feasibility of data collection was determined by the child's engagement and comprehension of the coloring task. Feasibility of behavioral coding protocol was determined by the ability to complete the full scoring protocol for each child.
S1 spent 25% of the time coloring and 75% holding the crayon. S2 spent 53% of the time coloring. S1 broke crayons on 57% of trials; 75% of breaks occurred while holding the crayon off the paper. S2 broke crayons on 77% of trials; 96% of breaks occurred while coloring. With multiple trials of the same crayon, both subjects increased their duration of coloring before break, S1 increased by a mean of 9.3 sec (SD=5.59); S2 increased by a mean of 7.45 sec (SD=7.07).
Administration of the protocol was feasible. Both subjects engaged in the task and behavioral coding data has the potential to examine force perception thresholds. However, the children's interactions with the crayons were different. The young child predominantly held the crayon, while the older child colored with the crayons. Development of age specific force perception thresholds may be needed given the differences in children's coloring interest and ability across the first 5 years of life.

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Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.15/N37

Topic: E.04. Voluntary Movements

Support: NIH Grant 9491952

Title: Hand movements are high dimensional

Authors: *Y. YAN[1], J. M. GOODMAN, JR[1], S. J. BENSMAIA[2];
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Abstract: The hand - an extraordinarily sophisticated and versatile organ - is our primary means for interacting with objects. Despite its staggering complexity, hand control is precise and effortless. A compelling hypothesis for how the brain manages to achieve this level of dexterity is that it restricts its control of the hand to a smaller, more manageable subspace than the full range of movements of which the hand is capable. This subspace can be broken down into sets of coordinated movement primitives termed synergies. A relatively small number of synergies can account for much of the variance in hand kinematics, consistent with the interpretation that kinematics are restricted to this subspace. Whether the remaining dimensions of hand movements are structured - and thus under volitional control - has not been investigated. To fill

this gap, we measure - using a camera-based motion tracking system - hand kinematics as human participants perform several manual tasks, namely grasping, typing, and finger spelling in American Sign Language. We then perform a principal components analysis (PCA) on the measured kinematics, as has been previously done, and explore the generalizability of high-variance and low-variance principal components. We also implement machine learning techniques to extract object-specific or sign-specific information from hand postures. First, we find that hand synergies differ across paradigms. Second, lower-variance principal components are systematically structured, suggesting that they are under volitional control rather than reflecting experimental or motor noise. Then, we measure the hand kinematics and neuronal responses evoked in primary motor cortex as two non-human primates perform a grasping task. Again, we find that lower-variance principal components carry object-specific information in both the kinematics and neural data. We conclude that volitional hand movements and their neuronal representation occupy a high-dimensional space.

Disclosures: Y. Yan: None. **J.M. Goodman:** None. **S.J. Bensmaia:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.16/N38

Topic: E.04. Voluntary Movements

Title: Walking and texting: Neuromuscular control during smartphone manipulation

Authors: P. K. ACHARYA[1], A. W. VAN GEMMERT[1], ***S. A. WINGES**[2];
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Abstract: Walking while holding a smartphone is one of many everyday tasks requiring predictive control strategies to maintain balance while modifying grip forces to respond to expected inertial forces due to the transport of the object. Additionally, texting on the smartphone while walking adds another layer of complexity because one has to maintain the grasp while allowing the digits to interact with the smartphone. To understand how the motor system solves the challenges posed by the complexity of the task, we investigated whether the neuromuscular control strategies differ between transporting an object and transporting an object while texting. To address whether strategies changed we examined muscle activity during smartphone manipulation while standing and walking, which allowed us to test two specific hypotheses: 1) hand and arm muscle activity will increase during a tapping task regardless of walking condition, and 2) hand and arm muscle activity will increase as walking speed increases. Eight healthy college students participated in the study. Passive markers were used to track whole body motion including specific segments of the right-hand thumb and smartphone.

Surface electromyograms (EMG) were recorded from the right and left trapezius, the three heads of the right deltoid, and nine right upper limb muscles. Subjects executed five different Tasks including one no-tap task and four tapping tasks where they tapped individual letters or a series of letters over the keyboard on the smartphone device using their right thumb. These five tasks were executed during four Movement conditions (MCon) including standing and walking at 80, 100, and 120% of their comfortable walking speed on a treadmill. Repeated measures ANOVAs revealed significant effects of Task for all hand and wrist muscles, biceps and the anterior deltoid muscle ($P < .05$); muscle activity was increased for tapping tasks. Significant effects of MCon were found for all extensors in the forearm, proximal arm muscles, and the first dorsal interosseous ($P < .05$). Standing compared to walking at any speed was associated with smaller amounts of muscle activity. When walking speed increased, muscle activity trended to increase as well, although only in proximal arm and trapezius muscles. MCon did not interact significantly with Task for any measurement. It is concluded that arm muscle activity increases are associated with speed increases while tapping increases all muscle activity of the upper extremities. Furthermore, the increased complexity as result of tapping and walking speed does not change the neuromuscular strategies active for walking and tapping tasks independently.

Disclosures: P.K. Acharya: None. **A.W. Van Gemmert:** None. **S.A. Winges:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

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Topic: E.04. Voluntary Movements

Support: NIH Grant R01NS085122
NSF CBET-1804550
NIH Grant R01HD53801

Title: Response to transport perturbation during reach-to-grasp in virtual environment

Authors: *M. P. FURMANEK[1,2], M. YAROSSI[1], M. MANGALAM[1], S. ANTHONY[1], S. MACIEL[1], L. F. SCHETTINO[3], S. V. ADAMOVICH[4], E. TUNIK[1];
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Abstract: In order to successfully reach to and grasp an object, the brain must control both transport of the hand to the object and preshaping of the fingers to grip the object. Classical theory suggests these two components are coordinated in parallel via two independent visuomotor channels. However, there is recent empirical evidence that motor control for reach

and grasp may be coupled. Here, we investigated how a mechanical perturbation of reach influenced preshaping of grip aperture. We hypothesized that if indeed reach and grasp are independent this mechanical perturbation would have no influence on the preshaping of grasp aperture as hand approaches the object. Using a custom virtual environment, five subjects (28.3 ±9.01 years) reached to grasp a virtual object. All subjects participated following IRB approved informed consent. On 25% of trials, resistive or assistive force (200 ms duration, 2, 4, 6N magnitude) was applied to the wrist 200 ms following movement onset using a robotic manipulandum. Mechanical perturbation of transport increased or decreased peak transport velocity during when applied in an assistive and resistive way, respectively. Critically, aperture scaled with changes transport velocity in direction and magnitude dependent manner. Following the perturbation response, the aperture trajectory returned to the unperturbed pathway. These preliminary results indicate a relationship in the coordination underlying the transport and grasping components of a reach-to-grasp movement. Understanding the relationship between reaching and grasping will provide useful insight for robotic/prosthetic applications to optimize efficiency in object grasping.

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Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.18/N40

Topic: E.04. Voluntary Movements

Support: R21 Grant NS095873

Title: Finger force perception during pressing tasks, Comparison of force matching and psychophysical reports

Authors: *C. J. CUADRA[1], M. L. LATASH[2];
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Abstract: We explored a recently introduced scheme of perception based on the concept of iso-perceptual manifold (IPM) in the combined afferent-efferent space of neural signals. Within this scheme, we assume that afferent (sensory) signals from multiple sources are estimated within a frame of reference provided by the multiple ongoing efferent processes that can be adequately described as time-varying spatial reference coordinates. An IPM is equivalent to stable perception of a physical variable. We used force-matching tasks between the two hands, and verbal reports, to explore finger force perception in a two-finger pressing task. The main

hypothesis was that accuracy would be lower and variability higher during individual finger force matching in a two-finger task compared to one-finger tasks. The subjects produced accurate force levels under visual feedback by pressing with either two fingers or one of the fingers of a hand (task-hand). They tried to match the total two-finger force or individual finger forces by pressing with the other hand (match-hand, no visual feedback). Also, we used verbal report within a psychophysical scale on the level of force that the task-hand was producing. The match-hand showed higher inter-trial force variability during single-finger matching when the task-hand performed the two-finger task compared to trials when the task-hand performed single-finger tasks. The match-hand overestimated the force of the task-hand at low forces and underestimated it at high force. The verbal report consistently overestimated the task-hand force, with larger errors for higher forces. These findings confirm our main hypothesis by showing that perception of individual finger forces can vary in multi-finger tasks within a space (IPM) corresponding to veridical perception of total force. Matching hypothetical commands to fingers, rather than finger forces, could be responsible for the force overshoots.

Disclosures: C.J. Cuadra: None. **M.L. Latash:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

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Program #/Poster #: 491.19/N41

Topic: E.04. Voluntary Movements

Support: NIH/NINDS NS083377
Program in Occupational Therapy

Title: Skill learning with the left non-dominant hand is predicted by interhemispheric connections to right superior parietal lobule

Authors: *B. A. PHILIP[1], M. P. MCAVOY[2], S. H. FREY[3];
[1]Occup. Therapy, Washington Univ. Sch. of Med., St. Louis, MO; [2]Radiology, Washington Univ. Sch. of Med., Saint Louis, MO; [3]Psychological Sci., Univ. of Missouri, Columbia, MO

Abstract: Movement of the left non-dominant hand is primarily driven by the right (contralateral) motor cortex, but previous studies have shown an increased role of the left (ipsilateral) hemisphere during skill learning and execution of demanding tasks. However, the mechanism and role of left hemisphere influence on right hemisphere remains unknown. Here, 22 healthy right-handed adults (15 female, age 29 ± 11) underwent resting state functional connectivity (FC) magnetic resonance imaging before 10 days of training on a left hand precision drawing task. We explored our data to identify pre-training interhemispheric FC that predicted subsequent post-training left hand performance. 86% of participants successfully improved their

left hand movement smoothness across training. These training-related increases in movement smoothness were predicted by pre-training FC between left primary motor cortex normative hand area (M1-hand) and right superior parietal lobule (SPL), and between left intraparietal sulcus (IPS) and right SPL. These two right SPL targets were restricted in size (0.66 cm^3 connected with left M1-hand, 1.46 cm^3 connected with left IPS), but still overlapped: shared voxels comprised 46% and 22% of the volumes, respectively. Therefore, the acquisition of precision skill with the non-dominant left hand seems to involve FC between a specific area in the right SPL, and left hemisphere areas involved in precision movement (left M1) and hand choice (left IPS). If confirmed, this pathway may reflect a key neural mechanism supporting skilled movement with the left non-dominant hand: specifically, a transcallosal route by which the right hemisphere capitalizes on left hemisphere specializations. These findings present a first step toward identifying new rehabilitation opportunities for patients with persistent impairment of their right dominant hand.

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Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

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Program #/Poster #: 491.20/N42

Topic: E.04. Voluntary Movements

Support: Prodex, ESA

Title: Moving objects upside-down: The robustness of dexterous manipulation

Authors: *L. OPSOMER[1], F. CREVECOEUR[1], J.-L. THONNARD[1], J. MCINTYRE[2], P. LEFEVRE[1];
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Abstract: In 1987, during a live performance in Tacoma, Mötley Crüe's drummer amazed the audience by having his entire kit revolve to play his solo upside-down, thereby proving theatrically that motor adaptation to reversed gravity is possible. Performing skilled movements in an upside-down position requires not only a reprogramming of the motor patterns to perform the same task as in upright position; it also involves an update of the forward model that predicts the changes in load at the fingertip resulting from arm motor commands. Previous studies suggest that the effects of gravity are taken into account to optimize motor behavior and are estimated anticipatively with the use of an internal model. Due to the permanent and ubiquitous nature of gravity on Earth, the prior on gravity direction is very strong. We then wondered how fast the kinematics and dynamics of arm movements can adapt when the orientation of the body with respect to gravity is reversed relatively to the usual upright position and if that adaptation

leads to after-effects. We approached these questions in the context of finger-arm coordination during object manipulation. Eighteen subjects participated in the experiment, which consisted of rhythmic arm movements performed along the feet-to-head axis and with a manipulandum held in precision grip. All participants performed 6 blocks of 20 arm oscillations in the *Upright* (head up) position, followed by 16 blocks in the *Upside-down* (feet up) position and finally 10 blocks back in the *Upright* position. Grip dynamics was assessed by means of the offset, gain, correlation and lag of the grip force (GF) - load force (LF) relationship. Our results show a great robustness of the grip-load force correlation and synchronization in the face of a reversal of body orientation. More specifically, from the first block in *Upside-down* position the gain of GF modulation was similar to the one in the *Upright* position and the lag between GF and LF remained close to zero. Moreover, no after-effect was observed following the 16 blocks performed in the *Upside-down* condition. Subjects coped with being upside-down by increasing the mean level of GF. Overall, this robustness of the grip-load force coordination shows that the orientation of the body with respect to gravity is taken into account to properly estimate future changes in LF during GF planning. Notwithstanding, grip dynamics were progressively tuned more finely with practice in the *Upside-down* position, as evidenced by an increasing correlation between GF and LF and a decrease in the mean level of GF during the five first blocks.

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Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.21/N43

Topic: E.04. Voluntary Movements

Title: Artificial proximity sensation using transcutaneous electrical stimulation improves force control at telerobotic operations

Authors: Z. ZHAO[1], *M. YEO[1], S. RYU[2], H. PARK[1];
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Abstract: Sensory feedback plays a pivotal role in enhancing the control accuracy of teleoperation by providing information about the object under manipulation and its environmental interaction. In robotic surgery, to improve the control accuracy of surgical robotic arms, visual feedback of the operation site is provided with a magnified high-definition 3D camera. However, such visual feedback has a line-of-sight problem, and further, the processing of rich visual information can add cognitive loads to surgeons. For these reasons, visual feedback might not be optimal, especially when the surgery involves delicate organs with the intricate

vessel or nerve arrangements. To regulate force accurately at contact, additional sensory information on the distance between the end effectors and organs is necessary. To address the unmet need to deliver distance information to surgeons, we incorporate an artificial proximity sensation to the teleoperation system. We hypothesize that the proximity sensation enhances the accuracy, reduces the initial force level, and shortens the time for handling sensitive objects. To test the hypothesis, we employed a robotic gripper and a wooden board with two force sensors to mimic the pinch operation in robotic surgeries and a sensitive object, respectively. During the test, we asked subjects to telerobotically pinch the object located along the line of sight, with minimum force on both fingertips. The distance information, between each side of the gripper and the object, is delivered to the operator's fingertip by a pulsing sensation with a frequency proportional to the distance. After the contact, we discretely increase the stimulation frequency to the level for subjects to feel as constant tingly sensation instead of pulsing sensation. Three types of sensory feedback were tested and compared: only visual feedback, visual feedback with numbers indicating the distance, and visual feedback with artificial proximity sensation. Experimental results demonstrate that subjects can pinch the board with the smallest force on each fingertip when the artificial proximity sensation is provided. This result suggests that adding artificial proximity sensation can improve force-control performance during robotic surgery.

Disclosures: **Z. Zhao:** None. **M. Yeo:** None. **S. Ryu:** None. **H. Park:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.22/N44

Topic: E.04. Voluntary Movements

Title: Sensorimotor rhythms during action observation are sensitive to experience but are not associated with skilled performance

Authors: *K. A. FERCHO[1,3], T. J. BOSCH[1], R. M. HANNA[2], L. A. BAUGH[1];
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[3]FAA Civil Aerospace Med. Inst., Oklahoma City, OK

Abstract: Neural activity over sensorimotor brain regions within the alpha (8-13 Hz) and beta bands (14-22 Hz) is modulated when an observer views actions. This activity is dependent on the observer’s experience with the action being observed, as well as recent experience with the observed object. However, little is known about the functional significance of this activity for skilled motor performance and the relationship between the object type and sensorimotor activity. This study used EEG to answer the following: 1) Do different types and amounts of sensorimotor experience with objects differentially alter alpha and beta band event-related

desynchronization (ERD) during observation 2) Do differences in alpha or beta activity correlate with skilled motor performance? Participants (N = 140) watched a short video showing an actor lifting objects with which they had varying levels of experience: a toothpaste tube (Common), a brass block (Familiar), or a yellow plastic block of unusual density (Novel). Next, participants gained experience by performing 300 lifts with the same objects (Extensive) or two lifts with the same object and 298 lifts of distractor objects (Brief). Participants then viewed the same short video. Thus, participants were assigned to 1 of 6 groups: 1) Common Extensive; 2) Common Brief; 3) Familiar Extensive; 4) Familiar Brief; 5) Novel Extensive; or 6) Novel Brief. Alpha and beta activity over C3 was analyzed for baseline and post-lifting action observation. Motor performance was assessed through an analysis of load phase duration. At baseline, there was greater beta suppression for the Common object when compared to the Novel object. Post-task, an Object x Experience interaction was found; for those in the Extensive experience group, there was more beta suppression for the Common object compared to the Novel object. However, recent experience only affected beta suppression for those in the Novel object condition, with increased beta suppression for Brief compared to Extensive groups. There was no significant effect of object or experience on alpha activity. Lifting kinematics revealed the most efficient lifts were observed for Common objects, followed by Familiar, and then Novel objects. Post-task beta band suppression was correlated with load phase duration for the Novel Extensive group, indicating increased beta suppression was associated with less efficient lifts. Therefore, increased beta suppression does not correspond with skilled motor performance. Beta activity may reflect a particular sensitivity and attentional bias to the somatosensory aspects of novel objects in an object lifting task, in addition to neuronal processing efficacy.

Disclosures: **K.A. Fercho:** None. **T.J. Bosch:** None. **R.M. Hanna:** None. **L.A. Baugh:** None.

Poster

491. Sensorimotor Transformation: Reach and Grasp

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 491.23/N45

Topic: E.04. Voluntary Movements

Title: Teleoperated robotic hand can tell size and softness of the object without vision, if force feedback from finger joints and tactile feedback from the fingertips are provided

Authors: *S. MANOHARAN, H. PARK;
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Abstract: Technology has been steadily increasing in complexity over the past few decades. Tools become to have more features and more degrees of control that increases the learning time for the operators. By repetitive usage, operators acquire intuitiveness in controlling the complex tools. However, at the initial stage of learning, high cognitive load should be involved. We

hypothesize that the initial learning process can be accelerated by multisensory feedback provided from the tools to the body. Earlier studies like the rubber hand and robotic hand experiments showed that multisensory feedback, composed of visual and tactile feedback, could establish a sense of ownership of a rubber glove. To test the hypothesis, we employed a robotic hand having independently-controllable 5-digits, and a glove with built-in electrodes that provides multisensory feedback to the tip of each finger. The robotic hand is controlled by subject's finger movements, as a master-slave control. The multisensory feedback is composed of visual feedback, tactile feedback, and force feedback. We added force feedback as the robotic hand can experience resistance when it grabs an object. For the visual feedback, the operator sees the real-time motion of the robotic hand as a low-latency mapping of their finger movements. For the second feedback, 5-tactor system is incorporated for tactile feedback using electrical stimulation. For the third feedback, force feedback system is incorporated for each of subject's fingers using an exoskeleton, in order to emulate the force experienced by the robotic hand. We tested the basic operation of the control of robotic hand along with the multisensory feedback capability. Subjects were asked to distinguish the four objects, as wooden/foam spheres and wooden/foam cubes. With both force feedback from finger joints and tactile feedback from the fingertips, teleoperated robotic hand can tell the size and softness of the object without vision, while it cannot without either force or tactile feedback.

Disclosures: S. Manoharan: None. **H. Park:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.01/N46

Topic: E.04. Voluntary Movements

Support: VISTA

Title: That's not my hand: Attributing errors to external sources dampens predictive but not proprioceptive changes in hand position estimates

Authors: *R. Q. GASTROCK[1,2], S. MODCHALINGAM[3,2], C. M. VACHON[1,2], B. M. 'T HART[2], D. Y. HENRIQUES[3,2];
[1]Psychology, [2]Ctr. for Vision Res., [3]Kinesiology & Hlth., York Univ., Toronto, ON, Canada

Abstract: People account for the source of motor errors when adapting to dynamic conditions within the environment or their own body. Adapting reaches to altered visual feedback of the hand involves updating hand position estimates based on changes in proprioception and efferent-based predicted sensory consequences, where predictions are computed by internal forward models based on the outgoing motor command. Our recent work showed that shifts in hand

position estimates persist, despite knowledge of the external nature of the perturbation. However, such explicit knowledge should allow for the brain to attribute the source of errors externally and not shift hand position estimates. Here, we manipulated the extent of external error attribution in four ways while participants trained with a 30 degree rotated hand-cursor: the 1) “non-instructed” control group received neither instructions nor different visual stimuli, 2) “instructed” group received a counter strategy for the rotation, 3) “cursor jump” group saw the cursor misalignment mid-reach on every trial, 4) “hand view” group saw both their actual hand and misaligned cursor on every trial. During training the instructed group immediately countered the rotation, while other groups showed typical learning rates. During reaches without visual feedback of the cursor, participants either included or excluded any strategy developed to counter the rotation. Only the non-instructed group could not do so at will, suggesting a lack of explicit awareness of the perturbation. Moreover, reach aftereffects for the hand view group were lower compared to the other groups. Participants also estimated the location of their unseen hand before and after training. They either generated their own movement, allowing for hand localization with both proprioception and predictions, or the robot moved their hand, leaving only proprioception. We found that shifts in predicted sensory consequences were dampened for the hand view group, but proprioceptive recalibration persisted in all groups. Furthermore, we found that proprioceptive shifts correlated with reach aftereffects. Thus, although groups differed with error attribution to the cursor, we speculate that proprioceptive recalibration is not based on the hand but on the cursor.

Disclosures: R.Q. Gastrock: None. **S. Modchalingam:** None. **C.M. Vachon:** None. **B.M. 't Hart:** None. **D.Y. Henriques:** A. Employment/Salary (full or part-time):; NSERC.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.02/O1

Topic: E.04. Voluntary Movements

Support: VISTA
Ontario Graduate Scholarship

Title: Implicit components of learning and the two-rate model

Authors: *J. E. RUTTLE[1,4], B. M. 'T HART[2,5], D. Y. HENRIQUES[3,4];
[1]Psychology, York Univ., North York, ON, Canada; [2]Ctr. for Vision Res., York Univ., Toronto, ON, Canada; [3]Dept Kinesiol & Hlth. Sci., York Univ., North York, ON, Canada; [4]Ctr. for Vision Res., North York, ON, Canada; [5]Ctr. for Vision Res., North york, ON, Canada

Abstract: People are very good at correcting their reaching movements based on error feedback. It is believed that there are at least two processes that are involved in this error-based learning. Some processes of adaptation have been well explained by a two-rate model proposed by Smith et al., 2006, which includes a fast and slow process, that respond differently to errors, and combine to change motor output, including those changes seen during rotated visual feedback training (McDougle et al., 2016). This model is specifically able to explain a rebound to a previous performance when error feedback is removed. Unfortunately, this model does not acknowledge the two other changes that occur either as a product of motor learning or as a driving force of motor learning; changes in hand estimates and reach aftereffects. These two changes are thought to be implicit as they persist even when the perturbation is removed, participants have no visual feedback, or they are told to ignore the perturbation. Here, we tested how vision during training plays a role in changes in hand estimates and compared the time course of reach aftereffects to the slow process. First, it appears that continuous feedback of the cursor and thus increased exposure to the visual-proprioceptive mismatch between the hand and cursor leads to larger changes in hand estimates than when exposed to impoverished visual feedback during rotated cursor training. Second, the participants show less of a rebound and do not seem to retain their previously learned states for as long. Finally, regardless of the instructions given to participants about how to execute reaches, reach aftereffects do not seem to match the time course of the slow process. In summary, the two-rate model cannot account for the commonly seen outcomes associated with motor learning and additional models may be required.

Disclosures: J.E. Ruttle: None. **B.M. 't Hart:** None. **D.Y. Henriques:** A. Employment/Salary (full or part-time):; NSERC.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.03/O2

Topic: E.04. Voluntary Movements

Title: Proprioceptive recalibration generalizes relative to hand position

Authors: *B. M. 'T HART, J. E. RUTTLE, D. Y. HENRIQUES;
York Univ., Toronto, ON, Canada

Abstract: People can quickly adapt their movements to various circumstances. When feedback on hand position is rotated around the start position, motor adaptation to this change is generalized to nearby reach directions, but peaks at the visual position of the trained target. In addition, our feeling of hand position is also recalibrated by altered visual feedback on hand position (proprioceptive recalibration). However, little is known about how these changes in felt

hand position generalize. In previous work with adaptation to a visuomotor rotation, proprioceptive generalization showed several distinct patterns. We observed 1) nearly uniform generalization, 2) generalization peaking around the direction of the visual training target and 3) generalization peaking closer to the trained movement direction (rotated relative to the visual target). What are the underlying causes of the differences in the generalization patterns? Those studies used different training and testing tasks. Interestingly, training paradigms or tests that were targeted at evoking or measuring recalibrated proprioception, seem more likely to result in a peak at the trained reach direction, as opposed to at the direction of the visual target. It is possible that the experienced proprioceptive signal is recalibrated, and the experienced signal should be close to the reach direction, not the visual target. This would predict that the direction of the rotation determines where generalization of recalibrated proprioception peaks. With a clockwise and counterclockwise 45 degree rotation, we find this is the case. The data on generalization of proprioceptive recalibration suggest that the training signals (sensory prediction error, motor or task error and visuo-proprioceptive discrepancy) have different effects on reach adaptation and proprioceptive recalibration, and these effects may be combined in distinct ways in different training and testing paradigms.

Disclosures: **B.M. 't Hart:** None. **J.E. Ruttle:** None. **D.Y. Henriques:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.04/O3

Topic: E.04. Voluntary Movements

Support: VISTA Doctoral Scholarship
Ontario Graduate Scholarship
NSERC CREATE: IRTG Brain in Action

Title: Unbounded implicit motor adaptation

Authors: *S. MODCHALINGAM[1,2], M. CICCONE[1], B. M. 'T HART[2], D. Y. P. HENRIQUES[1,2];
[1]Sch. of Kinesiology and Hlth. Sci., [2]Ctr. for Vision Res., York Univ., Toronto, ON, Canada

Abstract: When our intended movements have unintended outcomes, the human motor system can quickly adapt future movements. Motor output is modified in a way such that motor errors, that is, the difference between the expected and the perceived consequences of any motor output, are reduced. Both implicit and explicit components play key roles in adaptation. Explicit components, such as the use of conscious strategies to counter a perturbation, can be quickly employed and allow for flexibility in rapidly changing conditions. Implicit components on the

other hand, such as the unconscious updating of internal models, arise slowly and allow for reliable, persistent changes in the motor system. When adapting reaching movements, implicit components of adaptation have been demonstrated to have an upper boundary in the amount by which they alter future movements, regardless of the size of the experienced perturbation (Bond & Taylor, 2015); that is, they are thought to be limited in scope. Here, we reduce the motor errors experienced by participants when adapting their reaches to a visuomotor rotation, which increases in small steps. Consequently, we show that the recently proposed upper boundary on implicit adaptation can be overcome. This suggests that while implicit adaptation is difficult to achieve during tasks with large, salient errors, necessitating explicit strategies, in most natural situations implicit adaptation is sufficient and leaves costly cognitive resources free for other tasks. Bond, K. M., & Taylor, J. A. (2015). Flexible explicit but rigid implicit learning in a visuomotor adaptation task. *Journal of Neurophysiology*. https://doi.org/10.1152/jn.00009.2015

Disclosures: S. Modchalingam: None. **M. Ciccone:** None. **B.M. 't Hart:** None. **D.Y.P. Henriques:** A. Employment/Salary (full or part-time):; NSERC.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.05/O4

Topic: E.04. Voluntary Movements

Title: Network effects of cerebellar non-invasive stimulation: An MEG study on dystonic patients and healthy controls

Authors: *S. C. FICARELLA[1], A. RICHARD[2], Q. WELNIARZ[1], C. GALLEA[1,3,2,4], S. MEUNIER[2], E. ROZE[1,3,5], M. VIDAILHET[1,3,2,4,5];
[1]Hôpital Pitié-Salpêtrière, Inst. du Cerveau et de la Moelle épinière, Paris, France; [2]Sorbonne Universités, Paris, France; [3]Inserm U 1127, Paris, France; [4]CNRS UMR 7225, Paris, France; [5]Hôpital de la Pitié Salpêtrière, Paris, France

Abstract: Dystonia is a movement disorder characterized by abnormal muscular contractions and motor planning (Gallea et al., 2016). The cerebellum plays a critical role in dystonia (Lehéricy et al., 2013; Gallea et al., 2015) representing a potential therapeutic target (Tewari et al., 2017). However, the role of the cerebellum within the neuronal networks involved in movement planning is unclear. This study aims at investigating the network effects of cerebellar non-invasive stimulation during motor preparation. To this aim, 16 focal hand dystonia patients (FHD) and 19 healthy volunteers (HV) were included in the study with sham and cerebellar stimulation (transcranial magnetic for HV and transcranial alternating current stimulation for FHD). Participants performed a visuo-motor adaptation (VMA) task triggering cerebellar activity, before and after stimulation, while brain activity was recorded with

magnetoencephalography. Participants moved a joystick to reach a target with a cursor presented on a screen, under two different conditions. In the control condition, joystick's movements and visual feedback were related directly to the cursor's motions. In the deviation condition, visual feedback was rotated inducing trajectory error (curved), which participants had to correct to produce trajectories as straight as possible. While both sham and cerebellar stimulation significantly reduced errors in both groups, cerebellar stimulation significantly improved, compared to sham stimulation, the trajectory-correction learning rate in patients. Coherence measures between cerebellum and motor cortex for the beta frequency band correlate negatively with the learning rate. While the amplitude of trajectory errors was comparable between groups, HV adjusted their motor trajectories faster than patients and this learning rate was boosted by cerebellar stimulation compared to sham stimulation, more efficiently than in patients. This effect is likely due to a modulation of the coherence between the cerebellum and the motor cortex, in the beta frequency band. Cerebellar stimulation improved participants' learning rate, which depends on cerebellum-motor cortex communication. References 1.doi:10.1002/hbm.23315 2.doi:10.1002/mds.25527 3.doi:10.1523/JNEUROSCI.2300-09.2009 4.doi:10.1016/j.nicl.2015.04.013 5 doi:10.1002/mds.27123

Disclosures: S.C. Ficarella: None. **A. Richard:** None. **Q. Welniarz:** None. **C. Gallea:** None. **S. Meunier:** None. **E. Roze:** None. **M. Vidailhet:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.06/O5

Topic: E.04. Voluntary Movements

Support: VISTA graduate scholarship

Title: The effect of error-sensitivity and perturbation schedules on the slow and fast processes in reach adaptation

Authors: *A. T. BANSAL[1], B. M. 'T HART[2], D. Y. HENRIQUES[1];
[1]Kinesiology & Hlth. Studies, [2]Ctr. for Vision Res., York Univ., Toronto, ON, Canada

Abstract: Adapting movements to our ever-changing environment likely involves many neural processes, and the two-rate model (Smith et al., 2006) nicely demonstrates that at least two processes are at work, called the “fast” and “slow” process. It explains a rebound phenomena, where people revert to reaching as if they were still adapted to the initially learned rotation, when doing error-clamped trials after a short reversal of the adapted perturbation. Later work has mapped the fast and slow processes onto explicit and implicit learning, respectively. To test this link between the model processes and actual learning processes, we used a within-subjects

design where all participants (N=29) adapted to the same rotation introduced both gradually and abruptly (apropriately counterbalanced to prevent carry-over effects). Gradual rotations should rely on implicit learning more than abrupt rotations and lead to larger rebounds. However, we found no effect on either the size of the rebound or the fitted model's parameter values, suggesting that the two model processes may not directly reflect implicit and explicit learning. In a second experiment, all participants (N=35) did two of four conditions with abrupt rotation only (counterbalanced as before) where we varied both the duration of the reversal period (4 or 12 trials) and the amplitude of the rotation (aligned or reversed). Crucially, the initial learning phase is exactly equal, and should involve actual learning processes (both fast and slow) equally. We see no effect of the duration of the reversal period, but model parameters and rebounds change with the amplitude of the rotation in the reversal period. Consequently, the model predicts that the two processes are not equally involved in early learning, despite equal training. This further suggests that the applicability of the model is limited, as is fully in line with the conclusions of Smith et al. (2006). Furthermore, the first experiment was done with a stylus on a tablet in a laboratory setting and the second experiment using a regular mouse in a large computer room. Each experiment had one identical condition, to allow testing if two-rate paradigms may be done on regular PC's, and we found no decrease in performance.

Disclosures: **A.T. Bansal:** None. **B.M. 't Hart:** None. **D.Y. Henriques:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.07/O6

Topic: E.04. Voluntary Movements

Support: Burke Foundation 3654
NIH NINDS 5 R03 NS103070-02

Title: A supination task to assess corticospinal function in mice

Authors: ***S. F. AGGER**[1], N. SERRADJ[1], E. C. MEYERS[2], A. M. SLOAN[3], E. R. HOLLIS[1]; [1]Burke Neurolog. Inst., White Plains, NY; [2]Texas Biomed. Devices Ctr., Univ. of Texas at Dallas, Richardson, TX; [3]Vulintus, Inc., Louisville, CO

Abstract: In order to fully understand corticospinal circuit function in the learning and execution of skilled movements we have been working in concert with Vulintus, Inc. in order to develop a forelimb supination module for the MotoTrack mouse behavioral system. This task allows for repeatable, objective quantification of a stereotyped supination movement in an unbiased manner. Supination, the ability to turn the paw/hand from palm down to palm up, is critical for dexterity and is one component of the skilled reach behavior, a complex motor task used to

assess learning and recovery of skilled motor function.
Skilled motor control is affected by spinal cord injury and impairments of supination are characteristic of damage to the corticospinal tract, the direct output from neocortex to the spinal cord.
C57BL/6J mice, both male and female, had aluminum head plates attached at six weeks of age. Mice were water restricted and began training by eight weeks of age. Once mice learned how to turn a small knob with the assistance of the investigator, they began training daily using a stepped protocol with increased levels of difficulty. The degree of difficulty was determined by the counter weight and minimum turn angle. By the end of training mice were able to turn above a 10° threshold with a counter weight of 1g for at least 50 trials within a 15 minute session. Following completion of training, mice underwent unilateral transection of the left medullary pyramid (pyramidotomy). Testing was resumed one week post-pyramidotomy and continued twice weekly through eight weeks.

Disclosures: S.F. Agger: None. **N. Serradj:** None. **E.C. Meyers:** None. **A.M. Sloan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vulintus Inc. **E.R. Hollis:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.08/O7

Topic: E.04. Voluntary Movements

Support: SNSF P2EZP3_172128
SNSF P400PM_183904
NIH U19 NS104649

Title: Action discovery and refinement through reinforcement in the mouse corticostriatal network

Authors: *A. C. MOSBERGER, L. J. SIBENER, V. ATHALYE, H. F. M. RODRIGUES, R. M. COSTA;
Columbia Univ., New York, NY

Abstract: In novel action discovery, when an exploratory action leads to reward, credit is assigned to certain dimensions of the action, which are repeated, leading to refinement of the action over time. We are investigating how this mechanism unfolds in the corticostriatal network. Two distinct neuronal classes project from cortex to striatum, intratelencephalic (IT) and pyramidal tract (PT) neurons. Here we show that for the mouse forelimb circuitry, IT and PT cells are distributed across widespread cortical areas with specific distinctions in their locations.

These sensorimotor glutamatergic inputs from cortex to striatum are hypothesized to provide an efference copy of the planned and/or ongoing action, allowing the assignment of credit to the relevant action dimensions at corticostriatal synapses - a process that allows learning through reinforcement. To study this, we developed a novel joystick task, in which head-fixed mice can move a joystick in any direction on a 2D plane using their forelimb. Mice are trained to move the joystick from a predefined initial position to a target area in an uncued and self-paced manner. The training requires no external guidance except delivery of a reinforcer upon entering the target area and automatic returning of the joystick to the start position. After initial exploration within the 2D action space, mice gradually increase their accuracy and achieve high hit rates of 80% within 2 weeks. With learning, joystick trajectories become less tortuous, and more similar to each other, unveiling unprecedented forelimb control. Flow field analysis of the trajectories reveals a decrease in directional variability and a shrinkage of the used action space over time further indicating refinement of the action. To allow the repeated investigation of action learning, we change the location of the target area, requiring mice to discover the new target, and refine a new action through reinforcement. Using 2-photon imaging of anatomically distinct corticostriatal circuits of the mouse forelimb in combination with this joystick task we are currently identifying IT and PT neuronal dynamics of action discovery, credit assignment, and action refinement through reinforcement.

Disclosures: A.C. Mosberger: None. **L.J. Sibener:** None. **V. Athalye:** None. **H.F.M. Rodrigues:** None. **R.M. Costa:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.09/O8

Topic: E.04. Voluntary Movements

Support: NIH F31 NS111853
NIH U19 NS104649

Title: Thalamostriatal circuits in flexible and automatized motor skill execution

Authors: *L. J. SIBENER, A. C. MOSBERGER, H. RODRIGUES, V. ATHALYE, R. M. COSTA;
Columbia Univ., New York, NY

Abstract: Over the course of our lives, we learn to perform a variety of actions, which require exact motor control to be successful. Learning to perform a novel action starts with it being behaviorally flexible, and eventually transitions to automatized execution. We are investigating how this transition unfolds in the thalamostriatal network.

It has been shown that plasticity of glutamatergic inputs to the striatum are critical for motor learning. Previous investigations into striatal information integration have focused on glutamatergic cortical projections to dorsal striatum (DS), while largely ignoring glutamatergic input from the thalamus. The densest thalamostriatal projection come from the parafasicular nucleus (Pf), which projects widely to DS. Lesions of Pf produce deficits in goal-directed learning and reward devaluation. We hypothesize that Pf input into DS mediates flexible performance of motor skills.
To study the role of Pf during flexible motor skill execution, we developed a novel head-fixed joystick task, in which mice move an unrestricted joystick in a 2D plane. Mice learn to move the joystick from a set start position to one of two rewarded target areas. Over several sessions, mice increase their accuracy, and individual trajectories become shorter, less tortuous, and more similar, showing expert forelimb control. After ~2 weeks of training, we change the target location, requiring mice to switch from automatized executions to behaviorally flexible movements. Intra-session vector field analysis reveals an increase in variability and exploration within the action space shortly after the target switch. Then trajectories show the same refinement with the new target. We are now using 2-photon imaging of thalamostriatal circuitry to identify dynamics of this behavioral flexibility and refinement. These experiments are the first to dissect the role of thalamostriatal circuits in emergence of highly skilled forelimb control in mice.

Disclosures: L.J. Sibener: None. **A.C. Mosberger:** None. **H. Rodrigues:** None. **V. Athalye:** None. **R.M. Costa:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.10/O9

Topic: E.04. Voluntary Movements

Support: NIH Grant DP5-OD019897
NSF Grant DBI-1707398

Title: Reinforcement learning of continuous movements in the basal ganglia

Authors: *J. M. MURRAY, S. ESCOLA;
Columbia Univ., New York, NY

Abstract: --While the basal ganglia (BG) circuit has long been known to be involved in the learning and execution of voluntary movements, recent experiments involving multicellular recordings and optogenetic perturbations have made it possible to test at a more detailed level traditional assumptions about its role in action selection and sequencing and in the control of

movement vigor.
--To address the neural representations in BG underlying learned motor behaviors, we constructed a computational model of the BG circuit to implement reinforcement learning for a skilled reaching task. Unlike existing models of BG, the model operates in continuous space and time, without requiring that neurons exhibit pure selectivity for particular actions or that descending pathways through the BG are strictly parallel and action-specific.
--We then analyzed the neural representations that emerged in the trained network, including their relation to behavior and evolution during task learning. We found from this analysis that many of the prominent features of BG activity from recently published experiments could be recovered, including coactivation of direct- and indirect-pathway neurons at movement onset, positive correlation of both of these populations with movement vigor, and the evolution of transient dopamine signals as the task is learned. These modeling results provide a framework for interpreting existing experimental data and for generating predictions to be tested in future experiments.

Disclosures: **J.M. Murray:** None. **S. Escola:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.11/O10

Topic: E.04. Voluntary Movements

Support: Burke Foundation 3654
NIH 1 DP2 NS106663

Title: Corticospinal neuron function during skilled and unskilled forelimb training

Authors: *F. MARINO[1], N. SERRADJ[1], A. M. SLOAN[2], E. R. HOLLIS[1];
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Abstract: The corticospinal tract is the principal mediator of skilled motor control. Cortical motor representations (motor maps) depend on the underlying output of corticospinal and other corticofugal neurons. These maps are plastic and reorganize in response to skilled, but not unskilled, motor training. Modern optogenetic tools allow us to evaluate these networks by imaging endogenous activity of defined neurons over longitudinal studies. We used multiphoton imaging in concert with the MotoTrak isometric pull module (Vulintus, Inc.) to record the effects of skilled and unskilled training on corticospinal function. Mice 6 to 8 weeks old were injected with AAV2retro-GCaMP7f at cervical level 7 for retrograde transduction of corticospinal neurons with the genetically encoded calcium indicator GCaMP7f. Following transduction, mice received a cranial window implantation over exposed motor cortex and an affixed rectangular

aluminum head bar. Corticospinal neurons transduced with GCaMP7f were imaged using 2-photon microscopy during learning of our head-fixed skilled or unskilled forelimb behavior. Water restricted mice were trained daily on the isometric pull system. Training of our skilled task began with two weeks of behavioral shaping during which the target range for isometric pull was narrowed from 5-20 grams to 15-18 grams. After shaping, mice were trained for another two weeks to a minimum of 60% proficiency. Our unskilled isometric pull mice are trained over two weeks with an adaptive threshold which is calculated as the 50^{th} percentile of the previous 10 trials starting at a lower boundary of 5 grams. During training, neural activity was recorded to assess changes in motor networks during skilled or unskilled motor learning. After completing training, mice underwent bilateral transection of the medullary pyramids (pyramidotomy). Corticospinal neurons in the motor cortex were recorded twice weekly during testing post-injury to determine injury-induced changes in cell activity and motor networks. Images from recording sessions were preprocessed in FIJI to remove noise and further processed in MATLAB using constrained nonnegative matrix factorization (CNMF). This method consists of non-rigid motion correction followed by CNMF to select neurons and extract their fluorescent traces for analysis. These data are synchronized with output from our MotoTrak system to extract frames when the animal is actively pulling the lever. Normalized $\Delta F/F_0$ for each neuron is segmented by movement and identified as a successful or unsuccessful pull. Average corticospinal activity was compared between skilled vs unskilled movement both during training and post-injury.

Disclosures: F. Marino: None. **N. Serradj:** None. **A.M. Sloan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Vulintus, Inc.. **E.R. Hollis:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.12/O11

Topic: E.04. Voluntary Movements

Support: F.R.S.-FNRS, Belgium

Title: Learning adapted feedback responses to unpredictable force fields during reaching

Authors: *F. CREVECOEUR, J. MATHEW, P. LEFEVRE;
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Abstract: Motor adaptation results from the acquisition of novel representations in the nervous system allowing improvements of performance across a broad range of tasks. To date, there has been much emphasis on the acquisition of such patterns for predictable disturbances, and previous work highlighted that both prior and feedback control mechanisms share knowledge

about limb and environmental dynamics. Here we investigated whether healthy adults could learn to produce adapted feedback responses to unpredictable force field disturbances applied during reaching to address whether sensory feedback during movement could be used to adjust movement control. We instructed 18 healthy adults to perform reaching movements towards a visual target with a robotic handle (KINARM). On a random subset of trials (probability 1/3), we applied either an orthogonal field (lateral force proportional to forward velocity), or a curl field (force proportional and orthogonal to hand speed), both of clockwise or counter-clockwise directions, randomly interspersed with unperturbed trials. We found a reduction in path length across force field trials for both perturbations and directions, indicative of better compensation for the applied disturbance. An analysis of average surface activity from the main muscles involved in lateral corrections indicated that there was no systematic increase in co-activation, and highlighted a down-regulation of perturbation-related responses within 240ms of reach onset, which accounted for the improvement in online correction. Furthermore, the measured force at the handle became gradually better correlated with the commanded force, re-calculated offline based on the velocity profile of each trial. This increase in correlation was also observed in a standard adaptation paradigm performed as a control experiment (n = 8 participants), which confirms that it is a metric sensitive to adaptation. Together these observations indicate that feedback responses to unpredictable disturbances were tuned to the specific force profile experienced within each perturbation trial, and displayed similar improvements as in standard adaptation to predictable disturbances. These observations highlight that the nervous system adapts feedback control strategies within a trial to the experienced disturbances, and are consistent with the hypothesis of online adaptation during reaching.

Disclosures: **F. Crevecoeur:** None. **J. Mathew:** None. **P. Lefevre:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.13/O12

Topic: E.04. Voluntary Movements

Support: NSERC

Title: Single-pulse transcranial magnetic stimulation over the parietal cortex does not impair implicit visuomotor adaptation

Authors: ***F.-A. SAVOIE**[1], L. DALLAIRE-JEAN[2], F. THÉNAULT[2], K. WHITTINGSTALL[1], P.-M. BERNIER[2];
[1]Dept. de Médecine Nucléaire et Radiobiologie, [2]Dept. de Kinanthropologie, Univ. de Sherbrooke, Sherbrooke, QC, Canada

Abstract: Whether the parietal cortex contributes to the adaptation and maintenance of internal models (*i.e.* implicit adaptation) remains unclear. In a recent electroencephalogram study, Savoie et al. (2018) observed increased parietal activity in response to visuomotor sensory prediction errors in the hemisphere contralateral to the perturbed visual feedback, raising the possibility that the parietal cortex could sub-serve implicit adaptation. The goal of the present study was to causally test whether the phasic parietal responses reported by Savoie et al., which occurred 140 - 260 ms after the provision of visual feedback and peaked at location P4 of the 10-20 electrode system, were related to implicit adaptation. Participants reached toward one of two visual targets located on either side of a fixation point, while being pseudo-randomly submitted to a 45 degree visuomotor rotation. For left target trials, the rotation was clockwise so that the cursor feedback fell into the right visual hemifield, whereas the opposite was true for right target trials. On half of all rotation trials, single-pulse transcranial magnetic stimulation (TMS) was applied over either the right (P4, N = 14) or left (P3, N = 14) parietal cortex 150 ms after movement onset (*i.e.* the approximate moment of parietal response onset reported by Savoie et al.). To determine whether TMS influenced implicit adaptation, hand drift was compared on t trials that followed rotation with (RS+1) and without (R+1) TMS. It was hypothesized that interfering with parietal activity would reduce hand drift. Results revealed potent hand drift on post-rotation trials as compared to both rotation and null rotation trials (left target: p less than 0.002; right target: p less than 0.002, Bonferroni corrected), indicating that visuomotor rotation resulted in robust trial-by-trial behavioral updating, a reflection of implicit adaptation. Contrary to our hypothesis, however, neither left nor right parietal stimulation significantly impacted post-rotation hand drift for either target (left target: $p = 1.00$; right target: $p = 1.00$, Bonferroni corrected). These data suggest that parietal areas located under P3 and P4 are not critical for implicit adaptation. However, they may be important for other processes at play during sensorimotor adaptation, such as explicit adaptation, retention of motor memories, online control or proprioceptive recalibration.

Disclosures: F. Savoie: None. **L. Dallaire-Jean:** None. **F. Thénault:** None. **K. Whittingstall:** None. **P. Bernier:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.14/O13

Topic: E.04. Voluntary Movements

Support: NSERC Grant 418589

Title: Prior history of learning saturates the brain's capacities to form motor memories

Authors: *R. HAMEL[1,2], J.-F. LEPAGE[2], P.-M. BERNIER[3];
[1]Kinanthropologie, [2]Pediatrics, Univ. de Sherbrooke, Sherbrooke, QC, Canada;
[3]Kinanthropologie, Univ. De Sherbrooke, Sherbrooke, QC, Canada

Abstract: Learning rarely occurs in isolation from previous experiences. In fact, the brain's response to an ongoing event depends on its previous history of activity. Namely, a growing body neurobiological evidence now indicates that previous learning, by disrupting the brain's homeostatic state, can transiently saturate its capacity to undergo further neuroplastic changes. One ensuing possibility is that previous history of learning could ultimately impair retention of ongoing events. The objective of the present study was to test this possibility. For that purpose, three groups adapted twice to the same gradually introduced 21° visuomotor rotation, which occurred over two separate sessions. Given that prior learning-induced saturation was expected to be transient in time, the inter-session interval (ISI) was manipulated to either last 2min (n = 20), 1h (n = 20) or 24h (n = 20). For both sessions, retention was assessed immediately after adaptation through the persistence of biases in reaching behaviors during No Vision (i.e., vision of the cursor was occluded) and Washout phases (i.e., veridical vision of the cursor was provided). The main dependent variable was Hand Direction at PV (°). The hypothesis was that an ISI of 2min, as compared to a 24h ISI, would impair retention of the second as compared to the first session. Results indicated a three-way interaction that confirmed this hypothesis by ultimately revealing that retention was selectively impaired in the 2min ISI condition during the second as compared to the first session ($p = 0.013$; Cohen's dz = 0.652), while this effect was absent in both the 1h ($p = 0.940$; Cohen's dz = 0.017) and 24h ISI conditions ($p = 0.717$; Cohen's dz = 0.082). A control experiment (n = 20) and additional analyses further revealed that results could neither be accounted for by differing levels of adaptation prior to the assessment of retention nor, crucially, by physical fatigue. Verbal reports confirmed that the rotation remained unperceived for both sessions and for all groups. Globally, the present results suggest that the brain's capacity to form motor memories can be impaired by the previous history of learning, an effect that falls in line with the homeostatic constraints known to tightly regulate neuroplastic changes.

Disclosures: R. Hamel: None. **J. Lepage:** None. **P. Bernier:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.15/O14

Topic: E.04. Voluntary Movements

Support: NIH P01 NS083514

Title: Intensive motor learning induces EEG and behavioral changes that are reversed by a nap

Authors: *M. F. GHILARDI[1], **E. GIRAU**[2], S. RICCI[3], E. TATTI[4], C. CHAN[2], C. CIRELLI[5], G. TONONI[6];
[1]CUNY, New York, Italy; [2]CUNY, New York, NY; [3]Dept. Physiology, Pharmacol. & Neurosci., CUNY Med. Sch., New York, NY; [4]CUNY Sch. of Med., New York, NY; [5]Univ. of Wisconsin Madison Dept. of Psychiatry, Madison, WI; [6]Univ. of Wisconsin Madison, Madison, WI

Abstract: We investigated whether intense training in a motor adaptation task to rotated visual display induces neuronal fatigue in well-rested subjects and if a nap or quiet rest reverses such changes. 36 young healthy subjects performed 3 one-hour blocks of a reaching task with visuomotor learning (ROT), followed by a two-minute recording of sEEG with eyes open and by *mem* and *mov* tests, the former with working memory characteristics, the latter with motor features of ROT but without the learning component. At the end of the morning 20 subjects took a 90-minute nap, while 16 quietly rested for the same time. Similarly, 9 subjects underwent three blocks of simple reaching task (MOT). We found that intensive learning to adapt movements to new visuo-motor correspondences induced local power increases during spontaneous EEG over the cortical areas engaged by the task. After two one-hour ROT blocks power increased in the α range over a left fronto-central area and in the β range over a left centro-parietal cluster (mean±SE: 19±4%). A further block of ROT produced increases over a centro-frontal area (41±11%) in the θ range, in two symmetrical centro-parietal areas (left: 49±14%, right: 45±12%) in the α range, and over a cluster of electrodes in a centro-parietal area on the left (27±7%) in the β range. Also, in the frontal cluster, α and β power changes during the task positively correlated with θ power increases in sEEG3, suggesting that low frequency increases in sEEGs is related to learning activity. Such EEG changes were accompanied by an increasing number of errors when subjects performed *mov (*$p<0.001$), while performance in *mem* did not significantly change ($p=0.160$). Interestingly, MOT did not affect performance in *mem* ($p=0.787$) and only slightly improved *mov* ($p=0.020$), suggesting that the EEG effects of neuronal fatigue are related to learning. Local EEG changes, test performance and learning ability were renormalized by an afternoon nap but not an equivalent period of quiet wake. The frontal region, with the greatest increase after ROT, showed a significant power decrease in the 1-8 Hz frequency range only after the nap ($p=0.036$) but not after quiet wake ($p=0.540$). Additionally, *mov* performance improved only after a nap ($p=0.002$), while performance in *mem* did not change in either group. Finally, post-sleep improvements in *mov* were related to the nap δ; activity during N3 sleep ($r=0.82$, $p=0.002$). These findings suggest that specific neural circuits become fatigued with intense learning even without sleep deprivation. Restoration occurs only after a nap but after quiet rest of the same duration.

Disclosures: **M.F. Ghilardi:** None. **E. Girau:** None. **S. Ricci:** None. **E. Tatti:** None. **C. Chan:** None. **C. Cirelli:** None. **G. Tononi:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.16/O15

Topic: E.04. Voluntary Movements

Support: NIH P01 NS083514

Title: Practice in a motor learning task increases movement-related beta modulation depth over frontal and ipsilateral parietal areas in a subsequent motor test

Authors: *E. TATTI[1], S. RICCI[2], R. MEHRARAM[3], N. LIN[4], S. GEORGE[4], M. F. GHILARDI[4];
[1]CUNY Sch. of Med., New York, NY; [2]Dept. Physiology, Pharmacol. & Neurosci., CUNY Med. Sch., New York, NY; [3]Newcastle Univ., Newcastle upon Tyne, United Kingdom; [4]CUNY, New York, NY

Abstract: Modulation of beta oscillations (15-30 Hz) is a prominent phenomenon characterized by event-related desynchronization (ERD) during movement execution followed by a post-movement rebound (event-related synchronization, ERS) after the movement end. We previously found that beta modulation depth (ERS-ERD) increases with practice in an arm-reaching task. Such increases are likely to represent plasticity-related changes.
Here we investigated whether the magnitude of beta peak ERD, ERS and modulation depth is affected by previous practice with a visuomotor learning task. Subjects performed three 40-minute blocks with ROT (8 targets, 4 cm distance), a visuomotor adaptation task (28 subjects, age: 24±4) or MOT, a similar motor task without the learning adaptation component (14 subjects, 25±5). Before and after each block, both groups completed *mov*, a 5-minute reaching test with targets at 3 distances and 8 directions, without the adaptation component. High density EEG was recorded throughout the experiment. Mixed model repeated measures ANOVAs were run to test whether peak beta ERS, ERD and modulation depth over three regions of interest (ROIs, frontal, left and right parietal) differed across blocks and between task conditions. After both ROT and MOT, *mov* showed the greatest magnitude of beta modulation depth over the left parietal ROI, followed by the frontal and right parietal ROIs. Further, for all the ROIs, we found a progressive increase of beta modulation depth across the four blocks of *mov*, mostly over the left parietal ROI. Comparison between task conditions revealed that *mov* in the ROT condition was characterized by a steady, significant increase across blocks of beta modulation depth over the right and frontal ROIs, an effect that was not present during the MOT control condition. In general, the magnitude of beta modulation depth increased after the first block of MOT, but showed little change after the subsequent MOT blocks. Importantly, these effects were not accompanied by significant changes of motor performance indices during *mov*. Beta modulation

depth increase across blocks was mostly accounted for by changes in the ERS magnitude. In summary, increases of beta modulation across *mov* tests were more prominent after visuo-motor learning than after a simple motor task, especially over the right and frontal ROIs, areas that are involved in the learning task.
Since beta modulation might represent plasticity-related phenomena, these findings suggest that learning-related effects of prolonged practice in an implicit visuomotor adaptation task are carried over to subsequent motor tests in areas that are mostly involved in the specific learning.

Disclosures: E. Tatti: None. **S. Ricci:** None. **R. Mehraram:** None. **N. Lin:** None. **S. George:** None. **M.F. Ghilardi:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.17/O16

Topic: E.04. Voluntary Movements

Title: Consolidation of motor memory induced by instance-reliant learning

Authors: *M. JAVIDI, G. TAYS, S. BAO, *J. WANG;
Univ. of Wisconsin, Milwaukee, WI

Abstract: Motor adaptation, a type of motor learning, is thought to involve two distinct processes: algorithmic (or error-based) learning and instance-reliant (or use-dependent) learning. instance-reliant learning is a mechanism in which repeated performances of a motor task results in the accrual of motor instances that contribute to fast, automatized performances of the same task later. It has been shown that instances can be accrued not only during active performances of a motor task, but also during passive performances, which then can also be used to facilitate subsequent learning of a similar motor task that has not been experienced previously. While instance-reliant learning has implications for neurorehabilitation, it is unknown whether the effects of instance-reliant learning can persist over long periods of time. The objective of this study, thus, was to determine whether the facilitative effect of instance-reliant learning on visuomotor adaptation will last over several time delays (i.e., 5 minutes, 1 hour, 24 hours). The working hypothesis was that motor memory obtained as a result of instance-reliant learning will be consolidated to have a lasting effect for up to 24 hours. Neurotypical, right-handed young adults experienced four experimental sessions: baseline, passive training, time delay, and testing. All subjects became familiarized with a general targeted reaching task during the baseline session. In the passive training session, they received passive proprioceptive training of their dominant arm that was moved passively by an exoskeletal robot in a “desired” target direction (i.e., the direction to be learned later during the testing session) repeatedly. Following that, the subjects were randomly assigned into 3 groups: each experiencing a different time delay of either

5 minutes, 1 hour or 24 hours. In the testing session, the subjects performed reaching movements under a novel visuomotor condition, in which the visual display was rotated 30 degrees counterclockwise about the start circle. A group of control subjects were also tested, who experienced the baseline, 5-minute time delay, and testing sessions. Results indicate that all three experimental groups adapted to the rotation substantially better and faster than the controls. This demonstrates that motor memory obtained as a result of instance-reliant learning can be consolidated to have a lasting effect for at least 24 hours, which in turn suggests that an intervention protocol based on the idea of instance-reliant learning may be a viable option for improving arm motor function in stroke survivors, especially those with moderate-to-severe hemiparesis.

Disclosures: **M. Javidi:** None. **G. Tays:** None. **S. Bao:** None. **J. Wang:** None.

Poster

492. Human-Reaching Motor Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 492.18/O17

Topic: E.04. Voluntary Movements

Title: The nature of savings associated with a visuomotor adaptation task that involves either one arm or both arms

Authors: ***R. JAMES**, S. BAO, J. WANG;
Univ. of Wisconsin, Milwaukee, WI

Abstract: Visuomotor adaptation is a gradual process in which the nervous system adjusts the sensorimotor mappings in response to the changes in sensory inputs or environmental characteristics. Visuomotor adaptation usually results in savings, which refers to the phenomenon of faster relearning when exposed to a previously experienced condition later. The nature of savings is typically studied using a paradigm in which the same arm experiences multiple conditions related to savings (adaptation, deadaptation, readaptation). It has seldom been studied, however, using a paradigm that involves both arms. This is important, given that savings is observed not only when adaptation and readaptation occur with the same arm, but also when they involve both arms. Here, we investigated the nature of savings by examining how deadaptation with one arm, with or without visual Feedback (VFB), would influence the pattern of savings observed during readaptation with the same or the other arm. Neurologically intact young adults first performed targeted reaching movements under a 30-degree visuomotor rotation condition with the left arm. Following that, they were divided into six subject groups, who experienced additional conditions differently as follows: 1) deadaptation with the left arm (with VFB), then readaptation with the right arm; (2) deadaptation with the right arm (with VFB), then readaptation with the left arm; (3) deadaptation with the left arm (without VFB), then

readaptation with the right arm; (4) deadaptation with the right arm (without VFB), then readaptation with the left arm; 5) deadaptation with the left arm (with VFB), then readaptation with the left arm; (6) readaptation with the right arm (control condition). We hypothesized that if savings was associated with an internal representation that is effector independent, the pattern of savings observed during readaptation would be similar regardless of which arm was used during the deadaptation and readaptation sessions. Results showed that the amount of savings varied depending on which arm was used during the deadaptation session, and that the pattern of savings was not affected by the presence or absence of the visual feedback. Our findings suggest that internal representations developed following visuomotor adaptation involve some aspects that are effector independent (model-based, error-based or algorithmic learning) and other aspects that are effector dependent (model-free, use-dependent or instance-reliant learning); and they further suggest that the nature, or the amount, of savings can vary depending on whether it involves a single (e.g., one arm) or multiple (e.g., both arms) motor effectors.

Disclosures: **R. James:** None. **S. Bao:** None. **J. Wang:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.01/O18

Topic: E.04. Voluntary Movements

Title: Cognitive and sensorimotor contributions to the nine-hole peg test: A functional near-infrared spectroscopy study

Authors: *L. BONZANO[1], L. PEDULLÀ[1], G. BRICHETTO[2], M. BOVE[1];
[1]Univ. of Genoa, Genoa, Italy; [2]Multiple Sclerosis Italian Fndn., Genoa, Italy

Abstract: The Nine-Hole Peg Test (9-HPT) is used to measure finger dexterity in various neurological diagnoses, e.g., stroke, brain injury, Parkinson's disease and multiple sclerosis (MS). In this test, the subjects have to take the pegs from a container one by one and place them into the nine holes on the board, then to remove the pegs one by one and replace them back into the container.
The 9-HPT is usually considered as related to muscle strength and tactile sensitivity of the thumb, and proposed as gold standard measure of manual dexterity in MS research and clinical practice. However, it can involve cognitive aspects due to the "strategy" adopted to fill and empty the holes as fast as possible.
The aim of this work was to measure the 9-HPT performance in healthy subjects, while investigating task-related activity of prefrontal and sensorimotor cortical areas by functional near-infrared spectroscopy (fNIRS).
Twenty healthy volunteers were asked to perform the 9-HPT with their right (dominant) hand,

while recording changes in cortical oxy-hemoglobin concentration. The control condition (1-HPT) was defined by applying a paper mask, of the same color as the board, covering eight holes and leaving only the central hole visible: the subject had to take the pegs one by one, place them into the only hole on the board as fast as possible, and put them into a container close to the board.
We measured the time needed to complete the 9-HPT and the 1-HPT, and video-recorded the movements.
A block design was adopted, with three alternating task and rest periods for each condition (i.e., 9-HPT or 1-HPT).
The fNIRS study was conducted with two 8x8 channel-systems in tandem configuration (40 channels; source wavelengths 760nm and 850nm). The optodes were positioned over a cap based on the 10/20 EEG reference to cover cortical areas with a role in cognitive and sensorimotor functions, including Brodmann's areas 9, 10, 11, 3, 4, 6, 45, 44 and 40.
All participants completed the 9-HPT and the 1-HPT in less than 20 s.
On average, cortical activation was higher during the 9-HPT than the 1-HPT performance; the contrast analysis (9-HPT>1-HPT) revealed higher activation of bilateral prefrontal and left sensorimotor cortical areas during the 9-HPT.
Individually, the subjects following a regular pattern in filling and emptying the holes showed less activation; subjects adopting different strategies showed higher activation mainly located in the prefrontal areas.
In conclusion, the 9-HPT is commonly proposed as measure of hand dexterity but it involves complex functions. We suggest taking this into account when analyzing 9-HPT scores, especially in people with MS who can report cognitive and attentional deficits.

Disclosures: L. Bonzano: None. **L. Pedullà:** None. **G. Brichetto:** None. **M. Bove:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.02/O19

Topic: E.04. Voluntary Movements

Support: 03UH3NS095553

Title: Functional connectivity between thalamus, primary motor cortex, and primary sensory cortex in humans with essential tremor

Authors: *B. PARKS[1], E. OPRI[2], S. CERNERA[1], A. GUNDUZ[2];
[2]Biomed. Engin., [1]Univ. of Florida, Gainesville, FL

Abstract: Essential tremor (ET) is a hyperkinetic disorder that affects 0.9% of the population worldwide, and presents primarily as intention tremor of the bilateral upper limbs. Deep brain stimulation (DBS) has been shown to be clinically effective in reducing this tremor, but its mechanisms are poorly understood, necessitating studies that investigate functional connectivity between pertinent brain structures. The ventral intermediate nucleus of the thalamus (Vim) is a common target for DBS. During DBS surgery, we temporarily placed an electrocorticographic (ECoG) strip to record from the primary motor and primary sensory cortex, in addition to the Vim. We ran a simple cued motor task, which consisted of three states: rest, cue, and go. Separating out each trial into its respective condition, we calculated connectivity between the discrete structures described utilizing directed transfer function (DTF). To determine validity of connectivity values produced, surrogate analysis was performed. Average DTF values for connections between structures was then calculated, and connectivity values between conditions were compared for all structures using t-tests with p-values modified for multiple comparisons via false discovery rate (FDR). We discovered that connectivity between the Vim and the primary motor cortex differs in the strength of the connection between conditions. The difference in connectivity between conditions could lead to a more complete understanding of the motor system. Quantifying the functional connections that exist between deep brain structures and the cortex is fundamental for understanding the underlying mechanisms of DBS, together with improving the understanding of physiological movement.

Disclosures: B. Parks: None. **E. Opri:** None. **S. Cernera:** None. **A. Gunduz:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.03/O20

Topic: E.04. Voluntary Movements

Support: NSERC

Title: The effect of acute aerobic exercise on the consolidation of motor memories

Authors: *S. R. HOLMAN, W. R. STAINES;
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Abstract: Previous research has shown that acute aerobic exercise performed prior to motor training can assist with motor skill acquisition through enhancement of motor cortical plasticity. Recently, studies using high intensity interval training performed post-motor training have found improvements in the retention of the motor skill. This suggests that the timing of exercise relative to motor training is important to enhance motor memory consolidation, although the mechanisms are unclear. We hypothesized that acute moderate intensity exercise performed post-

motor training would also assist with motor skill retention and that this behavioural change would be positively correlated with neural markers of cortical plasticity post-exercise. Thirty three participants were randomly assigned to one of two groups: exercise (EXE) or control (CON). During the first visit, participants completed a motor training session of a bimanual wrist flexion task using left/right wrist movements to control the vertical/horizontal cursor position on a computer screen. Targets appeared in the upper left of the screen and the cursor appeared in the bottom right after 2 s to cue movement and generate a cortical movement-related potential (MRP). After motor training, participants in EXE performed a session of moderate intensity exercise on a recumbent bike for 20 minutes (70% of heart rate reserve). Participants in CON read for the same amount of time. Both groups completed two post-training tests after the exercise or rest: one 10 minutes after the exercise/rest session (Post 1), and one once heart rate returned to resting level in EXE (Post 2) or 30 minutes after rest in CON. Participants returned to the lab 1 day and 7 days later to complete retention and transfer tests of the task. MRPs were measured using electroencephalography (EEG) to investigate cortical plasticity related to motor performance and exercise during the first visit. Behavioural measures of speed and accuracy were collected at all timepoints as response time and root mean square of the difference in the actual from the ideal trajectory of the cursor. Preliminary analysis of behavioural data suggests that participants in EXE were able to retain the skill better than participants in CON. The EEG data demonstrates markers of cortical plasticity as an increase in the MRP amplitude from early to late training, which is consistent with previous motor training studies. The relationship of the changes observed over motor training to the adaptations post-exercise are being explored. These results may inform motor learning paradigms and future studies with other populations including older adults and neurorehabilitation patients.

Disclosures: S.R. Holman: None. **W.R. Staines:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.04/O21

Topic: E.04. Voluntary Movements

Title: The influence of the subjective estimation of force production on motor-related cortical potentials

Authors: *T. MIYAMOTO, T. KIZUKA, S. ONO;
Hlth. and Sport Sci., Univ. of Tsukuba, Ibaraki, Japan

Abstract: When the force was adjusted to a certain target level, the amplitude of the force is estimated by one’s sense of effort. It has been demonstrated that the subjective estimation of force (planned force) doesn’t always match to actual force when the visual feedback was not

available. Previous EEG studies have reported that the amplitude of motor-related cortical potentials (MRCP) increase in proportion to the magnitude of the force and the rate of force development. Those studies have given subjects the online visual feedback of a target level to produce a force, which indicates that the actual force is related to MRCP while the relationship between “the planned force” and MRCP is still uncertain. Since the motor imaginary evokes MRCP without overt movement, MRCP might be influenced by not only the actual force but also the cognitive process associated with force production. Therefore, in this study, the EEG was recorded under two conditions (blind and visual conditions) and two target levels (20 and 60% of maximal voluntary contraction [MVC]) to clarify the influence of the planned force on MRCP on the force production. Healthy males who are right hand dominant participated in this study. The isometric elbow flexion force was measured at 90° flexion. The force was produced as fast as possible (ballistic contraction). Under the blind condition, the force was produced at each target level (20 and 60%MVC) based on their subjective estimation without external feedback. Under the visual condition, the force was produced at each target level to the visual target line on oscilloscope screen. The blind condition was performed first, then the visual condition was performed to avoid the effects of visual feedback. The target levels were random order consisting of 50 trials per condition. The EEG was recorded from 20 electrodes according to the 10-20 positions. EEG signals were time-locked to the onset of agonist EMG. The results showed that there was a significant correlation between the actual force and the MRCP amplitude from the EMG onset to offset at frontal-central electrodes. In contrast, the MRCP amplitude prior to the EMG onset, which is related to motor preparation, showed no or slight significant correlation at same electrodes. These results suggest that cortical activities related to motor preparation could be influence by the planned force, which are not always associated with the actual force.

Disclosures: **T. Miyamoto:** None. **T. Kizuka:** None. **S. Ono:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.05/O22

Topic: E.04. Voluntary Movements

Support: NIH Grant R21-HD089731
SAFRI Explorer Grant

Title: Developmental aspects of predictive motor abilities

Authors: ***S.-W. PARK**[1], A. CARDINAUX[2], D. GUO[1], P. SINHA[2], D. STERNAD[1];
[1]Northeastern Univ., Boston, MA; [2]MIT, Cambridge, MA

Abstract: In motor control prediction is required for humans to interact with objects in the environment such as intercepting a ball, because signal transmission is too slow for feedback-based control. Although prediction is widely acknowledged as fundamental in computational models in human motor control, its developmental aspects have not yet been studied. This study devised a suite of interceptive tasks implemented in a virtual environment to examine predictive abilities of children and adults. Five virtual interception tasks were designed to examine different aspects of prediction with different degrees of challenge. In two tasks subjects moved a paddle to catch a virtual ball with the ball trajectory partially occluded, and to intercept to bounce the ball to hit a target. To reduce demands on motor coordination, two additional tasks used button pressing to test temporal and spatial prediction. In one control task subjects lifted the paddle to a static target as fast as possible (reaction time). The experiments were conducted in a research laboratory with thirty 7 to 12-year-old children and 14 young adults. In addition, the same experiments were stationed at the Museum of Science in Boston, where over 400 museum visitors across ages 5 to 92 performed the tasks. The task scores were analyzed in their development across age; the specific question was at what age the performance became indistinguishable from adults. Results showed that the catching ability improved with age and reached the level of adults at age 12. Children's performance differed depending on the degree of ball occlusion, but this sensitivity disappeared at age 10. The bouncing performance, which required control of impact position and velocity, reached adult level slightly earlier at age 10. Similar to the catching task, the performance of the two spatial and temporal prediction tasks became indistinguishable from adults at age 12. In contrast, the reaction time of the children participants continued to develop beyond age 12. The results at the museum were largely consistent with the in-lab results validating the robustness of the test paradigms. Taken together, the results identified developmental aspects of the ability to execute sensorimotor functions that involve prediction. The results also provide normative data to study predictive motor impairment in children with developmental disorders, such as autism spectrum disorder.

Disclosures: S. Park: None. **A. Cardinaux:** None. **D. Guo:** None. **P. Sinha:** None. **D. Sternad:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.06/O23

Topic: E.04. Voluntary Movements

Support: NIH-R01-HD045639
NIH-R01-HD081346
NIH-R01-HD087089
Northeastern University Undergraduate Research and Creative Endeavor Award

Title: Extrinsic noise benefits skill acquisition and timing accuracy

Authors: *A. CAHILL, Z. ZHANG, S.-W. PARK, D. STERNAD;
Northeastern Univ., Boston, MA

Abstract: When executing actions requiring accuracy such as target-oriented throwing, improvements with practice are typically characterized by decreases in error and variability or noise. However, advances in the physical sciences have demonstrated noise can also be beneficial, specifically by stabilizing, destabilizing, or masking undesired properties of a complex nonlinear system. This study examined the effects of adding noise to performance feedback in a motor task with the hypothesis that noisy feedback may exert "pressure" on the performer to suppress their intrinsic noise. Using skittles, a virtual target-oriented throwing task, subjects threw a virtual ball by rotating a lever arm and released the ball by lifting the hand from a force sensor to measure the time of release. In the virtual workspace, the ball was tethered to a vertical post and moved around the post with an elliptical trajectory determined by the angle and velocity of the ball at release. Error was defined as the minimum distance between the target and the ball trajectory. Mathematical analyses of the modeled task show redundancy, as an infinite number of angle-velocity combinations at release resulted in successful target hits, defining a solution manifold. Previous research showed that the arm trajectory can align with the solution manifold, creating a "timing window," reducing the demands on accurate timing of ball release. Additionally, "timing error" quantified the difference between the actual time of ball release and the time of release that would have achieved minimum error for each throw. By adding noise to the timing of ball release, we expected subjects to decrease their intrinsic noise and channel it into task-irrelevant dimensions.

Two groups of 10 subjects practiced skittles for 11 daily sessions. On days 3-8 the ball trajectory of the noise group was calculated from release parameters that were randomly selected from a range 10ms earlier or later than the veridical ball release time, modifying the ball trajectory displayed on-screen. Results showed that noise subjects performed significantly better than controls (using veridical release times for calculations). This success was primarily due to a decrease in timing error. Timing window did not increase, likely due to the specific geometry of the solution manifold. Importantly, they maintained this improved timing error on days 9-11 after the noise was withdrawn. These findings demonstrate that humans are capable of increasing their precision when extrinsic noise is present. Ongoing studies investigate the same noise manipulation in the task of bouncing a ball to examine how these beneficial effects of noise may depend on the task.

Disclosures: **A. Cahill:** None. **Z. Zhang:** None. **S. Park:** None. **D. Sternad:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.07/O24

Topic: E.04. Voluntary Movements

Support: MHRD Ucchatar Avishkar Yojana - BIO-18/19-309-MUAY-VSRV

Title: A cortico-basal ganglia model for choosing an optimal rehabilitation strategy for hemiparetic stroke

Authors: *S. ELANGO[1], S. V. CHAKRAVARTHY[1], S. JAYAKUMAR[1], R. NARAYANAMURTHY[1], V. MURALIDHARAN[2];
[1]Dept. of Biotech., Indian Inst. of Technol. Madras, Chennai, India; [2]Dept. of Psychology, Univ. of California San Diego, La Jolla, CA

Abstract: The major difficulty in designing an optimal motor rehabilitation strategy for stroke patients is the inherent contradictions that prevail in the existing intervention techniques (Hatem, Saussez et al 2016). To address this issue, we employ a cortico- basal ganglia model that can perform simple bimanual reaching tasks. The model consists of two components for each arm (right and left), comprising of an outer sensory-cortical loop and an inner basal ganglia loop that drives a simple 2-arm kinetic model to reach its respective target. These components are coupled at the level of their motor cortices by a coupling factor **ε**, thus facilitating bimanual arm movements. The reaching characteristics observed in the equidistant bimanual reaching study conducted by Rose and Winstein (Rose and Winstein 2004) have previously been captured by our model (Narayanamurthy et al, Bernstein Conference 2017). This model has now been extended to capture two other experimental paradigms from the same study namely congruent and incongruent aiming tasks. As observed in the experiment, the incongruent task setup under bimanual conditions showed an increase in the peak resultant velocity of the affected arm as opposed to the congruent task setup. This effect is attributed to the increased complexity and bimanual nature of the task setup. We also perform a comparative study between Constraint Induced Movement Therapy (CIMT), bimanual and unimanual reaching tasks and quantify their effect in terms of reaching error of the paretic arm as a function of distance (closest the arm can reach to the target) under two conditions of stroke: acute and chronic. It is observed that for lesions of smaller size, bimanual paradigm and for lesions of bigger size, both CIMT and unimanual paradigms prove to be more effective respectively. This effect is especially pronounced in chronic stroke condition. Thus, the model functions as a prototype test-bench for choosing a patient-specific rehabilitation strategy.

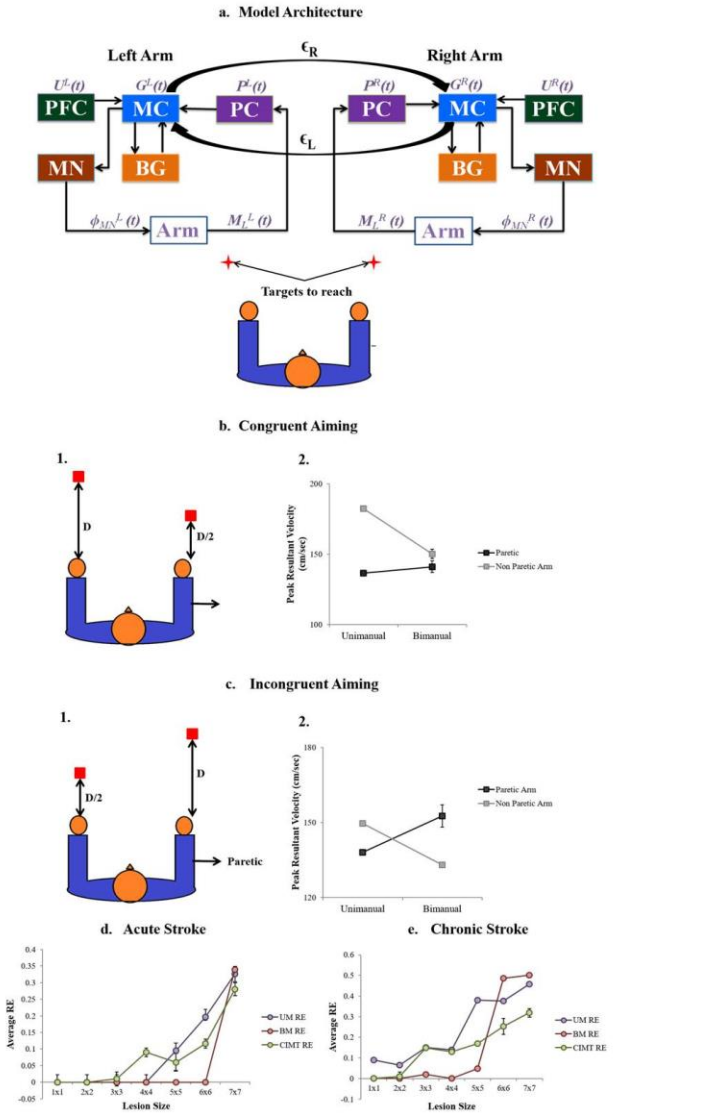

Figure: *A. Proposed Cortico-Basal Ganglia model architecture.* ***B. Congruent Aiming -*** *1. The task setup is shown. In this paradigm, the paretic arm has an easier (closer) target. 2. Peak Reaching Velocity (PRV) for both the arms are shown in unimanual and bimanual condition. In both cases, the non-paretic arm has higher PRV. C.* ***Incongruent Aiming -*** *1. The task setup is shown. In this paradigm, the paretic arm has a more complex (farther) target. 2. PRV is higher for the paretic arm under bimanual condition in this task setup. D. Lesion size vs reaching error in the case of acute stroke. E. Lesion size vs reaching error in the case of chronic stroke.*

Disclosures: S. Elango: None. **S.V. Chakravarthy:** 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.; MHRD Ucchatar Avishkar Yojana - BIO-18/19-309-MUAY-VSRV. **S. Jayakumar:** A. Employment/Salary (full or part-time):; MHRD Ucchatar Avishkar Yojana - BIO-18/19-309-MUAY-VSRV. **R. Narayanamurthy:** A. Employment/Salary (full or part-time):; MHRD Ucchatar Avishkar Yojana - BIO-18/19-309-MUAY-VSRV. **V. Muralidharan:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.08/O25

Topic: E.04. Voluntary Movements

Title: Gender differences in competitive anxiety and coping strategies in junior handball athletes

Authors: D. IVASKEVYCH[1], ***S. FEDORCHUK**[2], S. TUKAIEV[1];
[1]Lab. on Theory and Methodic of Sport Preparation and Reserve Capabilities of Athletes, Natl. Univ. of Physical Educ. and Sports of Ukraine, Kyiv, Ukraine; [2]Lab. on Theory and Methodic of Sport Preparation and Reserve Capabilities of Athletes, Natl. Univ. of Physical Educ. and Spor, Kyiv, Ukraine

Abstract: Competitive anxiety is related to athletes' performance. Due to this, it is important to maintain it on an optimal level. While anxiety has a well-studied gender difference that is related to the opposite patterns of activity in left parietal and temporal lobes, dorsomedial prefrontal cortex, cerebellum, and occipital gyrus, gender differences in competitive anxiety and its factors are not fully investigated. Coping strategies contribute to the decrease of psychiatric symptoms like depression and anxiety that supports an assumption of its importance for performance regulation. Exploratory research of competitive anxiety and coping strategies in Ukrainian junior handball national team was conducted. Participants of the study are 35 adolescences with mean age 15.63 (SD = 0.49). 13 participants were male, while 22 participants were female. Participants completed Ways of Coping Questionnaire (WCQ), which was developed by Folkman & Lazarus in 1988 and adopted by Bityutskaya in 2015, and Sport Competition Anxiety Test (SCAT), which was developed by Martens in 1977 and adopted by Hanin in 1982. Mean scores were: 8.74 (SD = 2.50) for Confrontive Coping, 8.22 (SD = 2.98) for Distancing, 13.63 (SD = 2.67) for Self-Controlling, 11.23 (SD = 3.22) for Seeking Social Support, 7.94 (SD = 1.93) for Accepting Responsibility, 9.86 (SD = 3.52) for Escape-Avoidance, 12.49 (SD = 2.97) Planful Problem-Solving, 13.49 (SD = 3.15) for Positive Reappraisal, and 19.02 (SD = 4.20) for SCAT. Female athletes scored 20.55 with SD = 3.63 on SCAT and 8.6 with SD = 1.92 on Accepting Responsibility scale. Male athletes received mean score 16.46 with SD = 3.95 on SCAT and 6.8 with SD = 1.36 on Accepting Responsibility scale. Female athletes have significantly higher scores on both SCAT and Accepting Responsibility scale of WCQ with $p=0.007$ and $p=0.006$ respectively. Cohen’s d was 0.47 for both tests. Spearman correlation test revealed moderate between SCAT scores and Accepting responsibility coping correlation $r = 0.39$ with $p = 0.02$ for the whole sample. Thus, accepting responsibility coping strategy is associated with increased competition anxiety in Ukrainian athletes. Both accepting responsibilities coping and competitive anxiety level are gender biased and are higher in female athletes but these gender differences have a moderate size effect.

Disclosures: **S. Fedorchuk:** None. **D. Ivaskevych:** None. **S. Tukaiev:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.09/O26

Topic: E.04. Voluntary Movements

Title: Perceptual modulation of the somatosensory system during planning

Authors: *A. DALIRI[1], B. MCGUFFIN[2];
[1]Col. of Hlth. Solutions, [2]Arizona State Univ., Tempe, AZ

Abstract: When we plan for movements, we also predict sensory consequences of our own movements; we use our predictions to prepare task-relevant sensory systems for their potential roles in sensory processing (Blakemore et al. 1998, 2000; Shergill 2003; Wolpert and Flanagan 2001). In the speech domain, we have shown that the speech motor system uses a similar mechanism to prepare the auditory system during speech planning (Daliri and Max 2018; Merrikhi et al. 2018). Such results are consistent with the fact that the speech motor system strongly relies on the auditory feedback (Guenther 2016). However, it is unclear whether the speech motor system also uses similar mechanisms to prepare the somatosensory system during speech planning.

In the present study (n=20), we developed a novel behavioral paradigm to investigate the modulation of the somatosensory system during speech planning. We measured the responsiveness of the somatosensory system at various time points during speech planning by delivering electrical stimuli to the lower lip. In two conditions (speaking and reading), participants were asked to judge whether they felt the near-threshold electrical stimuli (participant-specific intensity, 85% detection ratio at rest). In the speaking condition, participants overtly produced target words shown on a computer monitor. In the reading condition, participants read target words silently without any movement. We found that the detection ratio was attenuated during the speaking condition whereas it remained unchanged during the silent reading condition. This perceptual modulation gradually increased at time points closer to the onset of speech and was the largest during speech production.

Overall, our results suggest that the speech motor system prepares the somatosensory system during speech planning. These results are consistent with results of previous studies that have examined auditory modulation during speech planning (Daliri and Max 2018; Merrikhi et al. 2018; Mock et al. 2015), suggesting that the speech motor system may use similar mechanisms to prepare different sensory modalities.

Disclosures: **A. Daliri:** None. **B. McGuffin:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.10/O27

Topic: E.04. Voluntary Movements

Title: Visuospatial attention modulates motor cortex excitability

Authors: *S. BANDA, A. ANAND, S. CONVENTO, J. M. YAU;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Sensory processing guides our motor behaviors. To facilitate reflexive behaviors or to prime actions, visuospatial attention may automatically engage with the motor cortical system. Here we characterized the effects of visuospatial attention on motor cortex excitability. In two experiments, we delivered transcranial magnetic stimulation (TMS) over left motor cortex (M1) while measuring motor evoked potentials (MEPs) from participants' right hand. We manipulated participants' visuospatial attention using a challenging visual detection task performed on visual targets positioned near the left and right hands. In Experiment 1, we found that directing spatial attention near participants' right hand, even in the absence of visual cues, resulted in increased left M1 excitability. This result reveals the effects of endogenous visuospatial attention on M1 excitability. In Experiment 2, we qualitatively replicated the effects of endogenous visuospatial attention and characterized the effects of exogenous visuospatial attention and the temporal profile of acute visual influences on motor excitability. Our results imply that visuospatial attention automatically modulates motor cortex excitability. The automatic engagement of the motor system by visuospatial attention circuits conceivably results in faster and more precise motor behaviors.

Disclosures: S. Banda: None. **A. Anand:** None. **S. Convento:** None. **J.M. Yau:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

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Topic: E.04. Voluntary Movements

Support: This research was funded by the DFG (Deutsche Forschungsgemeinschaft) funded Collaborative Research Center on "Cardinal Mechanisms of Perception" (SFB-TRR 135).

Title: Neural correlates of error-prediction in the course of motor learning

Authors: *M. JOCH[1,2], L. K. MAURER[1,2], M. HEGELE[1,2], H. MAURER[1], H. MÜLLER[1,2]; [1]Justus Liebig Univ., Giessen, Germany; [2]Ctr. for Mind, Brain and Behavior - CMBB, Marburg and Giessen, Germany

Abstract: A forward model is a neural process that generates predictions based on sensory and efferent (e.g. information about motor commands in form of an efference copy) information. It is also assumed that forward model predictions are used for sensorimotor learning. However, we do not know how the forward model itself develops during learning. In the following experiment, we investigated the development of the forward model while learning a novel motor task using neurophysiological measures in the electroencephalogram (EEG).
Six participants trained on a semi-virtual goal-directed throwing task for 23 sessions with 400 trials each. To quantify the development of the forward model we recorded a neural potential located in mid-frontal brain regions, called error-related negativity (ERN, e.g. Falkenstein et al., 1991). The EEG was recorded in sessions 1, 5, 10, and 23. In addition, we analyzed the feedback-related negativity (FRN), which reflects processing of the terminal result feedback (i.e. hit or miss the target) and should behave complementarily to the ERN. The following results were calculated from a partial dataset. A complete dataset will be presented at the conference.
The behavioral results show a clear increase in task performance measured by the target hit rate (*S1*: 25%; *S5*: 48%; *S10*: 52%; *S23*: 62%). With respect to the neural correlates, we find an increase of the ERN mean amplitude over the sessions (*S1*: -.06μV; *S5*: -.07μV; *S10*: -.10μV; *S23*: -.32μV). Simultaneously, the FRN mean amplitude decreased (*S1*: -4.50μV; *S5*: -2.34μV; *S10*: -.75μV; *S23*: 1.17μV).
The development of the ERN and FRN mean amplitudes while learning a novel motor task suggest a shift error processing mechanisms. More specifically, early in learning, the control system relies more on information coming from external sensory feedback (larger FRN amplitude). With the increase of task performance, the forward model is able to generate more accurate outcome predictions. Thus, early information of outcome predictions is increasingly being used for error processing (larger ERN in late sessions). This points out that processing error information based on external feedback of the movement outcome is especially relevant when the movement outcome prediction is inaccurate and vice versa.
Falkenstein, M., Hohnsbein, J., Hoormann, J., & Blanke, L. (1991). Effects of crossmodal divided attention on late ERP components. II. Error processing in choice reaction tasks. *Electroencephalography and Clinical Neurophysiology*, *78*(6), 447-455.

Disclosures: **M. Joch:** None. **L.K. Maurer:** None. **M. Hegele:** None. **H. Maurer:** None. **H. Müller:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.12/O29

Topic: E.04. Voluntary Movements

Support: NSERC

Title: Interfering with potentiated actions produced by near-hand targets using rTMS

Authors: *A. PAOLETTI, M. SKELLEKIE, L. BROWN;
Psychology, Trent Univ., Peterborough, ON, Canada

Abstract: People display enhanced perception of visual targets when they are presented near hand. Research suggests that the near-hand effect relies on the same mechanisms that process visual information for action. According to the theory of affordances all objects afford a specific action, and there is evidence that simply viewing an object leads to the automatic generation of an associated potential motor response. It is possible that the generation of potential actions is enhanced when targets are located near one's hands. To investigate whether action potentiation drives the near-hand effect, participants were asked to respond to a target presented either near or far from a hand placed in the display. Participants completed this task both under normal conditions and under the influence of 1 Hz rTMS applied to the left motor cortex for 15 minutes, which should suppress actions potentiated by targets near the right hand. We found a significant right near-hand effect in both the control and rTMS conditions. For the left hand we found a significant near-hand effect in the control condition, but surprisingly it was reversed in the rTMS condition. We consider the possibility that right-hemisphere motor cortex activity - released from interhemispheric inhibition after rTMS suppression of the left motor cortex - may interfere with the near-hand effect. The action potentiation hypothesis is reconsidered within the context of these findings.

Disclosures: A. Paoletti: None. **M. Skellekie:** None. **L. Brown:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.13/O30

Topic: E.04. Voluntary Movements

Title: A cortical command circuit coordinates food handling and manipulation

Authors: *X. AN, H. MOHAN, K. MATHO, A. KEPECS, J. HUANG;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: In rodents and primates, food handling and manipulation using synergistic hand-mouth maneuvering is necessary for feeding and requires online sensorimotor coordination as well as dexterous motor control; the underlying neural circuits are not understood. We carried out a systematic optogenetic screen of pyramidal neuron (PyN) projection types and cortical areas that induce forelimb and orofacial movements in the mouse. We define a rostral forelimb orofacial area (RFO; centered around anterior 1.7mm and lateral 2.3mm), where activation of Fezf2 corticofugal PyNs (PyN^{Fezf2}) and PlexinD1cortico-striatal PyNs (PyN^{PlexD1}) induce highly coordinated forelimb and orofacial movements resembling feeding. We further reveal a caudal forelimb orofacial area (CFO; centered around anterior 0.3mm and lateral 3mm), where activation of Tle4 cortico-thalamic PyNs (PyN^{Tle4}) induce similar action, an effect dependent on functional RFO. Antero- and retro-grade tracing from these PyN types in RFO and CFO depict a highly connected cortical network involving primary and secondary sensory and motor areas of the forelimb and orofacial regions. This cortical network is embedded in the cortico-striatal-thalamic system, with outputs to numerous subcortical targets from midbrain, hypothalamus, to pons and spinal cord. Chemo- and opto-genetic inactivation of RFO and/or CFO PyNs impairs hand maneuvering and hand-mouth synergy during food handing, manipulation, and eating in head-fixed and free-moving mice. These results begin to implicate specific neuron types, cortical circuits and brain systems in sensorimotor coordination for object manipulation.

Disclosures: X. An: None. **H. Mohan:** None. **K. Matho:** None. **A. Kepecs:** None. **J. Huang:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.14/O31

Topic: E.04. Voluntary Movements

Title: Effect of chronic low back pain on movement inhibition using a Go/No-Go paradigm

Authors: *R. L. JUDY[1], W.-E. WANG[1], J. ALDERUCCIO[1], M. KLEIN[1], G. BRODY-HEIM[1], A. ANTONY[2], J. S. THOMAS[3], S. COOMBES[1];
[1]Applied Physiol. and Kinesiology, [2]Anesthesiol., Univ. of Florida, Gainesville, FL; [3]Virginia Commonwealth Univ., Richmond, VA

Abstract: Acute pain is a potent sensory signal that notifies the human body of immediate danger which can prime the motor system for action. For individuals with chronic low back pain (cLBP) movements often become slow, methodical, and rigid; typically displaying less variability in trunk-pelvis coordination, difficulty adapting to gait perturbations, less lumbar flexion, and freezing-like behaviors. Thus it is plausible that individuals with cLBP who experience movement evoked pain (MEP) would be better at inhibiting movement, but this hypothesis has not been directly tested. The purpose of this study was to investigate muscle activity during a Go/No-Go full-body reaching task in individuals with cLBP who do (cLBP-MEP) and do not (cLBP-noMEP) experience movement-evoked pain. Data was also collected from a pain-free control group (HC). We hypothesized that the cLBP-MEP group would be better able to inhibit movement and therefore make fewer errors during a Go/No-Go reaching task. Muscle activity was collected from the right deltoid as well as bilaterally from the thoracic longissimus, multifidus, and tibialis anterior during each trial. Participants wore a HTC Vive virtual reality (VR) headset where virtual targets were displayed. The task began with the appearance of a blue cube to cue subjects to get ready. If the target turned green, subjects had 750 msec to reach and touch the cube. If the target turned red, subjects had to inhibit movement. Location of the virtual targets were normalized to subject anthropometric characteristics to necessitate approximately 60 degrees of trunk flexion. A custom MATLAB program was used to identify errors during No-Go trials based on an increase in EMG activity above an individually determined threshold. A one-way between groups ANOVA found significantly fewer No-Go errors in the cLBP-MEP group compared to each of the other groups based on EMG activity in the right multifidus (RM) and the left tibialis anterior (LTA) muscles. Our observations suggest that movement-evoked pain is associated with better performance on a Go/No-Go reaching task, consistent with previous literature which links chronic pain with the inhibition of movement.

Disclosures: R.L. Judy: None. **W. Wang:** None. **J. Alderuccio:** None. **M. Klein:** None. **G. Brody-Heim:** None. **A. Antony:** None. **J.S. Thomas:** None. **S. Coombes:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.15/O32

Topic: E.04. Voluntary Movements

Support: NS 093695

Title: Noisier muscle activation exacerbates dysmetria in Friedrich’s ataxia relative to Spinocerebellar ataxia 6

Authors: *S. L. BRACKSIECK[1], A. CASAMENTO-MORAN[1], N. L. CLARK[1], B. YACOUBI KEYHANI[1], S. H. SUBRAMONY[2], D. E. VAILLANCOURT[1], M. CORTI[3], E. A.

CHRISTOU[1];
[1]Applied Physiol. & Kinesiology, [2]Neurol., [3]Pediatrics, Univ. of Florida, Gainesville, FL

Abstract: Dysmetria is a common symptom for Spinocerebellar ataxia type 6 (SCA6) and Friedrich's ataxia (FA). However, it remains unknown whether greater degeneration of the central nervous system in FA results in greater dysmetria than SCA6. Our purpose was to compare dysmetria in the two ataxias and determine whether increased CNS noise is a contributor to dysmetria differences. In addition, we determined the relationship between dysmetria and functional capacity of FA. Thirteen individuals with SCA6 and ten individuals with FA performed 50 trials of goal-directed contractions with ankle dorsiflexion while we recorded the EMG activity of the primary agonist (Tibialis Anterior; TA) muscle. We quantified the following: 1) dysmetria as the endpoint error during the goal-directed task; 2) CNS noise as the endpoint variability and the variability in the activation of the TA muscle; and 3) FA functional capacity as the score from the modified FARS clinical assessment. We found that FA exhibited greater dysmetria than SCA6 ($P < 0.01$) which was related to greater time endpoint variability ($R^2 = 0.47$). Greater time endpoint variability was associated with a more variable activation of the agonist muscle ($R^2 = 0.47$). Finally, greater dysmetria in FA correlated with their modified FARS score ($R^2 = 0.40$). Therefore, we provide novel evidence that the additional degeneration of FA relative to SCA6 results in a noisier activation of the agonist muscle, which impairs time control that leads to increased dysmetria and impaired functional capacity.

Disclosures: S.L. Bracksieck: None. **A. Casamento-Moran:** None. **N.L. Clark:** None. **B. Yacoubi Keyhani:** None. **S.H. Subramony:** None. **D.E. Vaillancourt:** None. **M. Corti:** None. **E.A. Christou:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.16/O33

Topic: E.04. Voluntary Movements

Support: ERC 742595

Title: Frontal cortical control of brainstem inhibitory neurons projecting to the intralaminar thalamic nuclei

Authors: *E. BOSZ[1,2], V. M. PLATTNER[1], M. A. DIANA[3], L. ACSADY[1];
[1]Inst. Exp. Med. Hung Acad Sci., Budapest, Hungary; [2]Semmelweis Univ., Budapest, Hungary; [3]Pierre at Marie Curie Univ., Paris, France

Abstract: Our previous data demonstrated that glycine transporter2 (GlyT2) positive neurons of the pontine reticular formation (PRF) inhibit the intralaminar thalamic nuclei (IL). Selective photoactivation of PRF-IL fibers evoked behavioural arrest for the duration of the stimulation. The strong motor response was surprising as PRF has been implicated in arousal but not in motor control. In the recent study, we aimed to examine the inputs of the PRF inhibitory cells probably carrying motor signals and the impact of these inputs on the activity of PRF inhibitory neurons. Retrograde tracer injected into the PRF labelled L5 pyramidal cells located in the cingulate and M2 cortices and neurons in the deep cerebellar nuclei. This connectivity is consistent with a possible motor functions but inconsistent with the presumed role in arousal. Injections of AAV-ChR2 into the frontal cortex of RBP4-Cre/Glyt2-eGFP double transgenic mice revealed that the entire PRF receives L5 inputs. Cortical afferents contacted mostly thick calibre dendrites of the GlyT2+ cells in the PRF. Juxtacellular recording and labelling in the PRF under ketamine/xylazine anaesthesia demonstrated that rhythmic activity of Glyt2+ cells was tightly linked to the slow cortical oscillation and was disrupted upon its spontaneous desynchronization. Pharmacological inactivation of the cortex led to decreased irregular firing of the GlyT2+ neurons. Photoactivation of M2 L5 cells evoked short latency action potentials with high probability in the PRF. These experiments indicate strong motor cortical control over the PRF-GlyT2 cells. In *in vitro* preparation optogenetic activation of M2 fibers reliably produced purely glutamatergic synaptic responses on PRF-GlyT2 cells. Both AMPA and NMDA receptors were functional at these synapses, which showed little short term depression during stimulation trains. Photoactivation of PRF-GlyT2 cells led to significant decrease in the firing rate of IL cells *in vivo*, suggesting that cortical activity may lead to decreased IL output in a selected cell population. To decide if the evoked behavior effect is purely motor related or has cognitive components as well we are doing *5 choice serial reaction time task*. If we activate the PRF-IL pathway we can examine if the cognitive abilities of the animal are impaired or the effect is purely motor related. Our results indicate that synchronous higher order motor (M2) cortical activity can reliably activate inhibitory neurons of the PRF, thus likely send a behavioural signal computed by frontal motor cortical regions. PRF GlyT2 cells in turn transfer this signal to the IL thalamus affecting thalamocortical and thalamostriatal activity.

Disclosures: E. Bosz: None. **V.M. Plattner:** None. **M.A. Diana:** None. **L. Acsady:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 493.17/O34

Topic: E.04. Voluntary Movements

Support: Albert Einstein Society, Albert Einstein Healthcare Network

Title: Visual and proprioceptive cuing differentially evoke two distinct routes for imitation

Authors: *M. W. ISAACS, L. J. BUXBAUM, A. L. WONG;
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Abstract: Imitation is an efficient means of rapidly learning new movements such as novel motor skills. This ability is often lost after a left-hemisphere stroke (apraxia), and deficits in imitation may be observed even in the ipsilesional (non-paretic) side. Such impairments may limit the ability to teach these patients new movement patterns during rehabilitation; hence patients with apraxia are among the poorest to recover following a stroke. What exactly is disrupted in these patients with imitation impairments remains unclear. One current hypothesis is that imitation involves the ability to reproduce desired body configurations; such representations are informed and updated by integrating visual and proprioceptive feedback of the limb. It is thought that the ability to plan body-configuration representations becomes disrupted by lesions to the inferior parietal lobule (IPL). In contrast, we have recently demonstrated the existence of an alternative route to imitation that specifies instead only the trajectory of the end effector; deficits in trajectory-planning have been associated with lesions to dorsal premotor cortex. Thus we hypothesize that patients may be impaired along either of these two routes, depending on the site of their lesion. To test this, we recruited a group of patients with left-hemisphere strokes and age-matched controls. Participants were asked to reproduce novel, meaningless gestures with their left (non-paretic, non-dominant) arm. Gestures were cued either visually by viewing the motion of a cursor to encourage trajectory-based planning, or proprioceptively without vision of the arm to encourage body-configuration-based planning. Participants also completed background tests to control for general proprioceptive, visual, or working memory deficits. We found that patients could be separated into two groups based on behavior: one group was moderately impaired at imitating both visually and proprioceptively cued movements relative to controls, while the other group was disproportionately worse at imitating proprioceptively cued movements. We observed that lesions associated with disproportionately poor proprioceptive imitation localized to the IPL, whereas patients that performed comparably in the two cuing conditions had more dorsal and frontal lesions, consistent with our hypothesis. This suggests that damage to the IPL results in an impaired ability to use proprioceptive information to plan body configurations during imitation.

Disclosures: M.W. Isaacs: None. **L.J. Buxbaum:** None. **A.L. Wong:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

Support: NIH/NIBIB (P41-EB018783)
NIH/NIBIB (R01-EB026439)
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NIH/NICHD (R25-HD088157)
NIH/NIMH (P50-MH109429)
US Army Research Office (W911NF-14-1-0440)

Title: Why don't humans always respond to a stimulus?

Authors: *L. MOHEIMANIAN[1,2], S. PARASKEVOPOULOU[1], P. BRUNNER[1,3], G. SCHALK[1,2,3];
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Abstract: The perceptual threshold is defined as the intensity of a stimulus that results in a response 50% of the time. Many previous studies have used stimuli around perceptual threshold to study different aspects of perception, but they have made little progress in understanding why people respond to stimulation in some trials but not others. Our work addresses this important neuroscientific question by recording electrocorticographic (ECoG) signals fromsensory and motor corticesin 6 human subjects that performed an auditory reaction time task. In this task, the subjects were asked to rapidly respond with a button press to a beep sound that was presented near perceptual threshold. As expected, the subjects responded to ~50% of all sounds. We set out to determine the specific neural mechanisms that could account for this variability in responses. We hypothesized that: 1) the transmission of sensory activity from sensory cortex to motor cortex is disrupted in trials in which no response occurred; and 2) variations in cortical excitability can explain these variations in transmission. To test our first hypothesis, we determined the cortical locations at which broadband gamma activity (a widely recognized marker of population-level cortical activity) significantly increased in response to stimulus onset. We then detected the onset of such broadband gamma activity in individual locations and trials, and quantified the fraction of all trials that had a detection at a particular location.Our results demonstrate that in trials that did not result in behavior, the number of detections decreases along the trajectory from auditory to motor cortex ($r = -0.56$, $p<0.001$). This decrease is not present in trials in which the subject responded ($r = -0.08$, $p>0.05$). To test our second hypothesis, we quantified cortical excitability (by measuring the instantaneous amplitude of low-frequency oscillations) at the time of broadband gamma onset, and did so separately for responded and missed trials. Our results show that cortical excitability is lower in trials that did versus did not result in behavior (38% increase, $p<0.01$). In summary, our study shows that when humans are presented with an auditory stimulus that is close to perceptual threshold, moment-by-moment fluctuations in cortical excitability determine whether population-level cortical responses to sensory stimulation are transmitted to motor cortex to produce a behavioral response.

Disclosures: L. Moheimanian: None. **S. Paraskevopoulou:** None. **P. Brunner:** None. **G. Schalk:** None.

Poster

493. Motor Learning: Circuits

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Topic: E.04. Voluntary Movements

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US Army Research Office (W911NF-14-1-0440)

Title: Temporal sequencing in the human auditory system

Authors: *J. R. SWIFT[1,2], G. SCHALK[1,3,2];
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Abstract: A number of recent studies have identified cortical areas within the human auditory system that are specialized for processing very specific types of sounds such as speech, language, or music. However, the specific temporal sequencing of processing in these areas is currently unknown, primarily due to technical limitations of the most prevalent imaging and analytic methods. Functional magnetic resonance imaging (fMRI) cannot resolve brain activity at the requisite temporal resolution (< 100 ms), and electro/magnetoencephalography do not have enough spatial resolution. A number of studies have demonstrated that recordings directly from the surface of the brain (electrocorticography (ECoG)) has both high spatial and temporal resolution, and have shown that ECoG is useful for neuroscientific investigations of the auditory system. Furthermore, practically all previous studies relied on cross-trial averaging of responses at individual locations, but this form of averaging blurs specific temporal sequencing due to the known temporal variance in responses. In our ongoing study, we are evaluating ECoG responses to auditory stimulation using a new method developed in our laboratory. This method can detect the onset of population-level cortical activity in individual trials, and facilitates highly accurate temporal localization of responses to auditory stimuli at individual locations. To date, we presented auditory stimuli to 15 epilepsy patients with implanted ECoG grids (76-250 channels), and applied single-trial onset detection to each location that responded to the auditory stimuli. In each location, we calculated this location's onset time as the median onset time across all trials. As expected, preliminary results localize auditory responses primarily to superior temporal

gyrus. The earliest cortical responses occurred around 130 ms after stimulus onset. Most importantly, preliminary results show a clear temporal progression from posterior to anterior parts of superior temporal gyrus. Current efforts seek to determine the specific temporal sequencing of cortical responses across different functionally distinct areas within auditory cortex.

Disclosures: J.R. Swift: None. **G. Schalk:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: E.04. Voluntary Movements

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CNPq (306817/2014-4 and 309560/2017-9
FINEP PROINFRA 2010 0.1.12.0308.00

Title: Kinematic changes in the uninjured limb after unilateral brachial plexus injury

Authors: L. SOUZA[1,2], G. FREIRE[1,2], J. MARTINS[3], L. LUSTOSA[1,2], T. POZZO[4], ***C. D. VARGAS**[1,2];
[1]Inst. of Biophysics Carlos Chagas Filho, Rio de Janeiro, Brazil; [2]Inst. of Neurol. Deolindo Couto, Rio de janeiro, Brazil; [3]Inst. of Neurol. Deolindo Couto, Rio de Janeiro, Brazil; [4]IIT@UniFe Ctr. for Translational Neurophysiol., Ferrara, Italy

Abstract: When reaching or moving an object from a standing position the brain has the challenge of stabilising upper limb movements while conserving postural balance. This complex task is done through the recruitment of motor synergies allowing to control our actions through the functional coupling of muscle groups. Traumatic brachial plexus injury (TBPI) causes important sensory and motor impairment of the affected limb. The objective of this study was to investigate if TBPI affects trunk/upper limb synergies through the kinematic recording of the uninjured limb. Eight volunteers with a severe unilateral traumatic BPI and nine age-paired healthy volunteers were invited to perform two different tasks while index finger kinematic parameters were measured. The first task consisted in, from a standing position, perform a series of reaching movements towards a homogenous surface located at a distance shoulder-surface of 120% of the arm's length upon which no specific endpoint was drawn. Results collected for the uninjured limb showed lower values for time to peak velocity (0.39%, SD 0.04 vs 0.47%, SD 0.04) and longer movement duration (1.71s SD 0.35 vs 1.48s SD 0.36s) in TBPI individuals

compared to healthy participants for the uninjured limb's index finger marker ($p < 0.01$), suggesting a higher cost for motor planning and execution after a TBPI unilateral lesion in this task. Furthermore, TBPI individuals presented lower index finger displacement (mean 68.39 cm SD 6.23) compared to those of healthy volunteers (70.98 cm SD 7.37, $p < 0.01$), which may indicate a strategy of minimising the upper limb movement amplitude to prioritise the conservation of balance. In a second task, the volunteers were asked to perform an elbow flexion/bringing a cup to the mouth movement in the upright position. Results showed lower values for time to peak velocity (Mean 0.37% SD 0.04 vs 0.40% SD 0.04, $p< 0.05$) in seven TBPI compared to eight healthy subjects for the uninjured limb's index finger marker, confirming that a unilateral TBPI lesion leads to higher cost in performing movements with the unaffected limb even when no explicit trunk movement is required. In conclusion, this study shows that severe unilateral TBPI affects the kinematics of the contralateral, unlesioned limb. These results point towards a higher cost in controlling trunk/upper limb movements in TBPI individuals compared to healthy individuals. In addition, it serves as a warning for the clinical community about the need of individualised therapeutic practices in TBPI to help reverse trunk and contralateral limb adaptations caused by the lesion.

Disclosures: **L. Souza:** None. **G. Freire:** None. **J. Martins:** None. **L. Lustosa:** None. **T. Pozzo:** None. **C.D. Vargas:** None.

Poster

493. Motor Learning: Circuits

Location: Hall A

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Topic: E.04. Voluntary Movements

Support: NIH P41-EB018783
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NIH U24-NS109103
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NIH R25-HD088157
P50-MH109429
US Army Research Office W911NF-14-1-0440

Title: How does the brain produce behavior? Advances in understanding of large-scale cortical physiology

Authors: *G. SCHALK;
Natl. Ctr. for Adaptive Neurotechnologies, Wadsworth Ctr, NYSDOH, Albany, NY

Abstract: Previous research has produced ample evidence that specific areas in the brain are remarkably functionally specialized, and that flexible behaviors are supported by coordinated dynamic interaction of these areas. At the same time, it is unclear whether these interactions follow fundamental principles that generalize across brain areas and different dynamic behaviors. We propose that, despite the known diversity in function and anatomy of different brain areas, many characteristics of dynamic behaviors (such as reaction time) can be explained by the moment-by-moment variations in cortical excitability and cortical excitation, and by five surprisingly simple principles that govern them. In my talk, I will describe these principles and will show results of modeling and experimental studies supporting them. Using modeling studies, I show how these five principles can explain: 1) the relationship between broadband gamma and oscillatory power and phase; 2) the relationship between oscillatory power/phase and response rate; 3) alpha frequency-dependent changes in reaction time; 4) the relationship between stimulus intensity and reaction time/response rate; 5) the differences in reaction time/response rate for unisensory vs. multi sensory stimulation; and 6) the differences in reaction time/response rate for congruent vs. incongruent stimulus presentation. Using experimental studies, I demonstrate that these principles can explain up to 41% of the single-trial variance in reaction time in a reaction-time task, and show that they can describe why people respond or do not respond to a stimulus presented at perceptual threshold.
In summary, there is increasing evidence that many human behaviors or experimental findings can be explained by surprisingly simple principles that appear to generalize to different behaviors and brain regions.

Disclosures: G. Schalk: None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.01/O39

Topic: E.04. Voluntary Movements

Support: NIH Grant NS23805

Title: A novel take on zona incerta efferent connections from axonal tracing mapped with PHA-L in the rat

Authors: *D. S. ZAHM[1], M. T. DESTA[1], S. SUBRAMANIAN[1], Y. TAN[2], K. P. PARSLEY[1]; [1]Pharmacol. and Physiol., [2]Surgery, St. Louis Univ. Sch. of Med., Saint Louis, MO

Abstract: Aside from Ricardo's classic autoradiographic study (Brain Res 214:43-60, 1981) and some subsequent regionally circumscribed descriptions, current understanding of the outputs from the zona incerta (ZI) is based mainly on retrograde labeling. Here, we report some

previously unappreciated features of ZI output organization revealed by mapping from focal injection sites with the sensitive anterograde tracer PHA-L. We find that ZI efferents arising from rostromedial (rm) clusters of A13 dopaminergic and melanin-concentrating hormone neurons (that we think were correctly regarded as aligning with the medial hypothalamus system - Sita et al., Neurosci 148:949-69, 2007) project successively less densely to the same structures from progressively more caudolateral (cl) ZI sites that lack A13 and MCH neurons, suggesting a rm-cl gradient. The vicinity of the A13 neurons is densely and preferentially targeted by projections arising more laterally in the ZI. Labeled fibers in neocortex (Lin et al., Science 248(4962):1553-6) are generally very sparse, although stronger after medial injections, and often ramify in cortical superficial lamina 1, consistent with origins as displaced lateral hypothalamic and/or ventromedial thalamus (VM) neurons. In the lateral habenula, mainly the caudal oval nucleus gets labeled input that is very dense after rm injections, but spare to negligible after more cl injections. Thalamic projections are patchy in intralaminar, LD, LP and PO nuclei and involve the whole of none of them in any given section. Dense ZI outputs to the superior colliculus (SC), labeled by injections into all but one ZI site, are diffuse in the rostral SC, but more caudally form discrete, wedge-shaped sectors with distinct densely labeled tri-partite bands over intermediate and deep SC cell laminae together with a deepest patch centered on the boundary between the periaqueductal gray and adjacent tegmentum. The exception was an injection into the boundary between the ZI and VM that labeled amongst the most numerous descending axons seen in the study, but virtually none in the SC, indicating either that output from the VM is not purely ascending, or ZI at the VM boundary region lacks a projection to the SC. Otherwise, all of our PHA-L injections into the ZI labeled projections that descend both to the SC and caudal brainstem, which challenges consensus that projections to the SC and brainstem arise preferentially, respectively, in ZI dorsal and ventral tiers. Together, these insights suggest a rm-cl differentiation of ZI and add new, functionally significant perspective to our understanding of ZI outputs that would have been unavailable other than with the aid of PHA-L.

Disclosures: **D.S. Zahm:** None. **M.T. Desta:** None. **S. Subramanian:** None. **Y. Tan:** None. **K.P. Parsley:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.02/O40

Topic: E.04. Voluntary Movements

Support: Science and Technology Commission of Shanghai Municipality 15JC1400104
111 Project Base B16018

Title: Spatial-temporal tuning properties of the rodent frontal orienting field neurons

Authors: *L. LI[1], Y. CHEN[1], H. CHEN[2], J. LI[1], C. MA[1], J. C. ERLICH[3];
[1]NYU-ECNU Inst. of Brain and Cognitive Sci. at NYU Shanghai, Shanghai, China; [2]Dartmouth College, Psychological and Brain Sci., Hanover, NH; [3]NYU Shanghai, Shanghai, China

Abstract: Overt attention, indicated by orienting sensors on the head towards the direction of interest in the environment, is critical for the animal's survival and success. Orienting has been extensively studied with sophisticated behavioral paradigms in primates. However, researches in rodents are mainly carried out with two-alternative forced choice(2AFC) tasks. Here we developed a novel multidirectional orienting task in rodents inspired by classic primate saccadic eye movement paradigms. In this task, the rat orients its head to various directions by nose-poking into one of the 7 ports on a vertical 2-D wall. The direction of a single or a sequence of orienting movements are guided by visual cues. Previous studies with 2AFC tasks have implicated the rodent frontal orienting field (FOF) as a key circuit element for spatial cognition. Here we recorded from the right FOF of a rat during the visually-guided orienting movements with 64-channel silicon probes. Over 30% of all identified neurons displayed directional selectivity between the visual cue onset and the movement, and the preferred directions of FOF neurons spanned across all 6 tested orienting directions. Direction selectivity of these neurons were either transient or lasting, and better aligned to either the visual cue or the movement. In some neurons, directional selectivity emerged around 70 ms after the visual cue onset, comparable to early visual response in primate FEF. We observed a subset of neurons tuned to orienting directions in an egocentric reference frame, yet there were also neurons whose firing rate were influenced by the task context of the movement. These results indicate that FOF is a critical node for the planning and execution of orienting movements, and will promote research in the neural basis of spatial cognition in the rodent model system.

Disclosures: L. Li: None. **Y. Chen:** None. **H. Chen:** None. **J. Li:** None. **C. Ma:** None. **J.C. Erlich:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.03/DP07/O41

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: E.04. Voluntary Movements

Support: ERC Starting Grant OptoMotorPath (338041)
cluster of excellence BrainLinks-Brain-Tools (EXC 1086)

Title: Real-time burst detection of neural oscillations allows behaviourally relevant neurofeedback

Authors: *G. KARVAT, A. SCHNEIDER, M. ALYAHYAEY, F. STEENBERGEN, I. DIESTER;
Freiburg Univ., Freiburg im Breisgau, Germany

Abstract: Neural oscillations as important information carrier in the brain, are increasingly interpreted as transient bursts rather than as sustained oscillations. Short (<150 ms) bursts of beta-waves (15-30 Hz) have been documented in humans, monkeys, and mice. These events were correlated with memory, movement and perception, and were even suggested as the primary ingredient of all beta-band activity. However, a method to measure these short-lived events in real-time and to investigate their causal impact on behaviour and overall oscillatory power is missing. Here we present a real-time data analysis system, capable to detect short and narrowband bursts. The system is associated with an operant conditioning apparatus for rodents, thus enabling closing the loop between oscillatory events and behaviour (neurofeedback). We successfully trained 3 rats to increase the beta event rate in motor cortex, and indeed observed an overall increase in beta-power, supporting the critical role of events on beta-band activity. The increase in beta could be linked to behaviour, as a machine learning algorithm could reliably predict occurrences of beta events based on the rats' movements. Our results demonstrate the potency and flexibility of the real-time neurofeedback system in freely moving rodents as well as the impact of transient bursts on global oscillatory power. Our approach can be a starting point for a plethora of studies targeted at understanding the causal role of oscillatory bursts. For example, instead of artificial external stimuli, real-time burst-triggered stimulus presentations could be combined with behavioural and electrophysiological measurements, thereby allowing to probe the intrinsic function of oscillatory bursts. Furthermore, neurofeedback has been clinically used for decades without a clear understanding of the underlying neural mechanisms. As our tool is ideally suited for rodents, it can be combined with additional invasive or non-invasive treatments and post-mortem histology, thereby providing a new testbed with high relevance for future clinical developments.

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Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

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Topic: E.04. Voluntary Movements

Support: cluster of excellence BrainLinks-Brain-Tools (EXC 1086)
RatTrack (BW-Stiftung)
Bernstein Award 2012 (01GQ2301)

Title: Marker free 3D tracking reveals insights into the role of the motor cortex in movement planning and execution in freely moving rodents

Authors: *A. SCHNEIDER[1], C. ZIMMERMANN[2], T. BROX[2], I. DIESTER[1,3,4];
[1]Optophysiology Lab., [2]Computer Vision Group, [3]BrainLinks-BrainTools, [4]Bcf, Univ. of Freiburg, Freiburg, Germany

Abstract: To study the role of motor cortex in movement preparation and execution in rodents, precise information about the executed movements is required. Previous approaches relied onto restricting the animal movements to a simplified, highly trained behavior or required the use of markers to track the unrestrained movements of the animal (Mimica et al. 2018). Key point detection via deep learning so far only allow 2D estimations of key point positions (Mathis et al. 2018). Here we introduce a network that is based on a multi-view approach via 7 cameras for the prediction of 3D positions of defined body parts. Predicting points in 3D removes the depth ambiguity and allows for experiments with unrestrained animals while minimizing self-occlusion of body parts. We manually annotated 12 key points (tail, nose, eyes, ears, front/hind paws) for training the model. Our network can be adapted to various behavioral tasks and subjects requiring only minimal human input by leveraging active learning. In order to precisely synchronize behavioral data with electrophysiological recordings we implemented hardware-triggered cameras (30 fps). With this combined approach, we recorded 3 rats (female, 1 Sprague Dawley and 2 Long Evans) with chronically implanted laminar 32 channel probes in motor cortex (front paw area, AP: 1.2/3.9 mm, ML: 2.3-2.4 mm) freely foraging in a transparent box. On average, we recorded 35 single units per session (total 317). 141 (44.5%) neurons were significantly modulated with movement (Welch t-test, Bonferroni corrected). Motor cortex contained information about several body posture variables, e.g. body pitch and head angle (linear regression: 47% and 9% explained variance, respectively). Interestingly, shifting the neural data relative to the behavior revealed that some variables were represented at different time lags. While body-pitch was best predicted at zero lag, front paw speed was best predicted with ~100 ms lag suggesting a planning role of the motor cortex. Our multi-view body pose estimation approach contains the unique combination of marker-free whole body movement estimation as well as precise movement tracking of individual body parts (e.g. front paws) in freely moving rodents in 3D. Thereby, the marker free 3D tracking method allows assessing the involvement of the motor cortex in movement planning and execution in unprecedented detail.
Mimica et al. (*Science* 2018) Efficient cortical coding of 3D posture in freely behaving rats.
Mathis et al. (*Nature Neuroscience* 2018) DeepLabCut. Markerless pose estimation of user-defined body parts with deep learning.

Disclosures: **A. Schneider:** None. **C. Zimmermann:** None. **T. Brox:** None. **I. Diester:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

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Topic: E.04. Voluntary Movements

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Simons Collaboration on the Global Brain

Title: Long-range connectivity does not predict functional response types in mouse anterior lateral motor cortex

Authors: *W. YANG, Z. DING, N. LI;
Baylor Col. of Med., Houston, TX

Abstract: Intermingled neurons in frontal cortex exhibit selectivity for sensory, motor, and cognitive variables. We examined behavior-related activity in mouse anterior lateral motor cortex (ALM) in relation to the structure of the underlying neural circuits. Mice performed a tactile decision-making task in which they used their whiskers to discriminate object locations and reported their choice using directional licking. We analyzed the spiking activity from over 6,000 ALM neurons. ALM neurons exhibited heterogeneous activity that correlated with the tactile stimulus, future movement, and other behavioral variables. Subsets of ALM neurons exhibited highly similar activity profiles over time. Based on the shape of the peristimulus time histogram, ALM neurons could be clustered into over 30 functionally distinct sub-populations. ALM could not maintain activity in isolation, rather, behavior-related activity is mediated by multi-regional interactions between ALM and connected brain regions (Svoboda & Li, *CONB* 2018). We examined the possibility that distinct ALM functional cell types are differentially driven by distinct long-range inputs. We related ALM functional cell types to long-range inputs from three brain regions that form multi-regional circuits with ALM - contralateral ALM (cALM), secondary somatosensory cortex (S2), and ventral-medial thalamus (VM). Silencing these brain regions produced qualitatively distinct effects on ALM activity: silencing VM abolished ALM activity in most neurons; silencing S2 silenced ALM activity mostly in the superficial layers; silencing cALM produced little change in ALM activity. These observations suggest that each long-range input has unique roles in mediating ALM dynamics.
To measure long-range connectivity, we modified ChR2-assisted circuit mapping (Petreanu et al,

Nat Neurosci 2007) and applied it *in vivo* to identify ALM neurons receiving direct inputs from each of the three brain regions. These postsynaptic ALM neurons were further analyzed in terms of their intrinsic and synaptic properties as well as their responses during the task. We found that long-range inputs indiscriminately targeted ALM neurons with respect to their functional cell types. ALM neurons coupled with each brain region were equally diverse as other non-coupled ALM neurons. Furthermore, we did not find any relationship between intrinsic properties nor synaptic properties of ALM neurons and functional response types during behavior.
These results suggest that the structure of long-range inputs is not sufficient to explain response types in frontal cortex.

Disclosures: **W. Yang:** None. **Z. Ding:** None. **N. Li:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.06/O44

Topic: E.04. Voluntary Movements

Title: The corticospinal tract is involved in sensory filtering but not motor command in the lumbar cord of rodents

Authors: *C. BICHARA[1,2], Y. MORENO-LOPEZ[1], M. CORDERO-ERAUSQUIN[1];
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Abstract: A well-coordinated movement relies on a properly planned motor command and the consideration of incoming sensory information: the “expected” inputs (when they are linked to the motor command itself) and the more relevant “unexpected” ones (that require correcting the ongoing movement). The cortex is involved in the control of both of these motor and sensory functions, and it has been recently hypothesized that it does so through a common pathway: the corticospinal tract (CST). The goal of this study is to unravel how the cortical filtering of sensory inputs hinges on the cortical motor command to produce well-coordinated voluntary motor behaviors. As serious motor afflictions can result from dysfunction of these circuits, their better characterization could unveil potential therapeutic targets.
First, we mapped the regions of the cortex that elicit muscle contractions and sensory filtering using photostimulation. Then, in the identified area, we injected a virus encoding for the trans-synaptic tracer wheat Germ agglutinin (WGA) fused to a cre-Recombinase along with a spinal cord injection of a virus encoding for Cre-dependent form of ChannelRhodopsin2. This allowed us to identify CST’s postsynaptic neurons in the spinal cord, to analyze their localization and nature, and to test the effect of their specific activation in vivo.
We first demonstrate that the same area of sensorimotor cortex evokes both muscular contraction and primary afferent depolarization (PAD), i.e. sensory filtering. We show that CST neurons

located in the area in charge of top down sensory-motor control project in the spinal cord onto interneurons located in the deep dorsal horn (lamina IV to VII). Importantly, their selective activation leads exclusively to PAD, but no muscle contraction.
This result suggests that while sensory filtering through PAD and muscular contractions originate from the same region of the sensory-motor cortex, they diverge in their pathways and reach different populations of neurons in the spinal cord. PAD is controlled by the CST whereas the motor command is indirect and convey its message through subcortical structures.

Disclosures: C. Bichara: None. **Y. Moreno-Lopez:** None. **M. Cordero-Erausquin:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.07/P1

Topic: E.04. Voluntary Movements

Support: KAKENHI 17H06309
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AMED JP19dm0107150

Title: Value information that affects decision making is transmitted from the thalamus to the motor cortex

Authors: E. YOSHIDA[1], K. NAKAE[2], K. KOBAYASHI[3], S. ISHII[2], *M. MATSUZAKI[1]; [1]Grad. Sch. of Med., The Univ. of Tokyo, Tokyo, Japan; [2]Grad. Sch. of Informatics, Kyoto Univ., Kyoto, Japan; [3]Natl. Inst. for Physiological Sci., Okazaki, Japan

Abstract: We can estimate the values of presented cues and decide whether to act after each cue presentation through operant conditioning. It is thought that the striatum is a critical region to estimate such cue values and that the motor cortex generates the motor command for the appropriate action. However, it is unknown whether and how cue value information estimated in the striatum is transmitted to the motor cortex, including the secondary and primary motor cortical areas (M2 and M1). Anatomically, the motor thalamus receives the projection descending from the striatum and sends axons to M2 and M1. We recently reported movement-related activity in thalamocortical (TC) axons projecting from the motor thalamus to M1 in mice performing a self-initiated lever-pull task (Tanaka et al., 2018). Here, we developed a new reward-based lever-pull task. In this task, one of two cues with different sound frequencies (cues A and B) was randomly presented in each trial. After a cue period, the mice chose whether to pull the lever with their right forelimb. When the mice pulled the lever, a water reward was delivered at a high probability in the cue A trial and a low probability in the cue B trial. After

training for this task, the mice pulled the lever more frequently in the cue A trial than in the cue B trial. During the task, we conducted two-photon calcium imaging of TC axons in the left M2 and M1. Activity of a subset of TC axonal boutons increased after cue A onset, while few boutons exhibited increased activity after cue B onset. Linear discriminant analysis revealed that the emergence of cue information transmitted by M2-projecting TC axonal boutons preceded that of cue information transmitted by M1-projecting ones. Channelrhodopsin-2 stimulation of M2-projecting TC axons during the cue period increased the frequency with which the mice pulled the lever in the cue B trial. These results suggest that M2-projecting axons of the motor thalamus transmit cue value information that can affect subsequent decision making.

Disclosures: E. Yoshida: None. **K. Nakae:** None. **K. Kobayashi:** None. **S. Ishii:** None. **M. Matsuzaki:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

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Program #/Poster #: 494.08/P2

Topic: E.04. Voluntary Movements

Support: NIH Grant 5R01HD084362-03
NIH NEI Training Grant 5T32EY015387-15
McDonnell Foundation Grant 220020516

Title: Intracortical microstimulation of sensorimotor cortex in short-tailed opossum (Monodelphis domestica): New insights into the evolution of motor cortex in mammals

Authors: *A. C. HALLEY[1], M. K. BALDWIN[1], M. ENGLUND[2], A. SANCHEZ[1], L. A. KRUBITZER[1,2];
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Abstract: The organization of the neocortex in some marsupials, such as the short-tailed opossum (*Monodelphis domestica*), is thought to reflect that of the earliest mammals. Early studies that utilized electrophysiological recording and cortical stimulation found that marsupials such as the Virginia opossum (*Didelphis virginiana*) appeared to have a single region of neocortex which contained both a sensory map of the face and body as well as motor map of the face and body. More modern studies using short-train intracortical microstimulation (ST-ICMS) in the short-tailed opossum found that only movements of the vibrissae and jaw could be elicited from a relatively small region of the somatosensory cortex that responds to cutaneous stimulation of the face (Frost et al., 2000). The absence of a separate motor area rostral to S1 in marsupials led to the hypothesis that early mammals exhibited a sensorimotor “amalgam” which is retained in living marsupials, but which was differentiated over eutherian evolution into separate M1 and

S1 fields (Lende, 1963). However, recent work in our laboratory has shown that long-train intracortical microstimulation (LT-ICMS) elicits movements from somatosensory cortex (not only from motor cortex and premotor cortex) in most eutherian mammals including primates, tree shrews and rodents. In this study, we utilized LT-ICMS to reinvestigate the types of movement that can be evoked from the neocortex of the short-tailed opossum. We found that movements could be elicited from a much larger region of cortex than in previous studies, and that movements included body regions other than the vibrissae and jaw, such as the hindlimb and forelimb. We also found evidence for an additional motor representation of the vibrissae that is rostral and medial to the classical area of sensorimotor overlap. These two vibrissae representations were separated by motor representations of the forelimb and hindlimb. Our results indicate that, as in other marsupials and eutherian mammals, S1 contains a complete motor representation of the body overlapping with the somatosensory cutaneous representation. Our finding of a separate rostromedial vibrissal motor region suggests there are at least two separate fields within cortex from which movements could be evoked, one corresponding with S1, and one in a rostral field, which could correspond to a primitive M1. Given the motor functions of S1 in eutherian mammals, we propose that early mammals exhibited S1 (rather than an undifferentiated "amalgam") and that a separate motor cortex was elaborated over the course of eutherian evolution.

Disclosures: A.C. Halley: None. **M.K. Baldwin:** None. **M. Englund:** None. **A. Sanchez:** None. **L.A. Krubitzer:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.09/P3

Topic: E.04. Voluntary Movements

Support: NSF Grant 1656882
NIH Grant NS058659

Title: Contribution of the ventro-lateral thalamus (VL) to the locomotion-related activity of motor cortex

Authors: *I. N. BELOOZEROVA;
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Abstract: The activity of motor cortex is closely related to strides and is necessary for accurate stepping on a complex terrain. How this activity is generated remains unclear. This is largely because we still do not know much about information motor cortex receives during locomotion and how it contributes to the formation of cortico-spinal commands. The ventro-lateral nucleus

of thalamus (VL) is the main source of the ascending projection from the thalamus to motor cortex, and its signals may be particularly important for shaping the cortico-spinal commands. The goal of this study was to clarify the contribution of signals from the VL to the formation of locomotion-related activity of motor cortex. In two chronically instrumented cats (a male and a female) we recorded the activity of neurons in layer V of motor cortex as cats walked on a flat surface and horizontal ladder. We first reversibly inactivated approximately10% of the VL unilaterally with a glutamatergic transmission antagonist CNQX and analyzed how the VL inactivation affected activity of neuronal subpopulations in motor cortex. We focused on neurons that contribute axons to the pyramidal tract (pyramidal tract projecting neurons, PTNs) or project to the red nucleus. We also studied subpopulations of neurons that have somatosensory receptive fields on different segments of the forelimb. In one of the cats we later lesioned 50-75% of the VL bilaterally with a neurotoxin kainic acid and recorded the activity of motor cortex over the next month. We found that contribution of the VL to the locomotion-related activity of motor cortex neurons is chiefly excitatory, fluctuates over the step cycle, and depends on the locomotor task. We further found that the VL contribution is larger to the activity of PTNs with slow- than fast-conducting axons, particularly during the complex task of ladder locomotion, when it accounts for nearly 100% of the slow-conducting PTNs' activity. We also found that during both simple locomotion on the flat surface and complex visually-guided stepping on the ladder, the VL contribution to activity of motor cortex neurons is limb segment-specific. The contribution is large to the activity of neurons related to the shoulder and elbow, and small for the wrist and paw-related cells. To the activity of the shoulder-related group, the VL contributes most during the transition from the stance to swing phase, and most heavily influences the elbow-related group during the transition from the swing to stance. The experiment with kainic acid lesions showed that these VL contributions are only partially replaced even when movements recover after the lesions.

Disclosures: I.N. Beloozerova: None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

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Topic: E.04. Voluntary Movements

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Whitehall Foundation
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Simons Collaboration on the Global Brain

Title: Modularity produces a robust neural code for motor planning

Authors: *G. CHEN[1], B. KANG[2], J. W. LINDSEY[2], S. DRUCKMANN[2], N. LI[1];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Stanford Univ., Stanford, CA

Abstract: Resilience to perturbations is a fundamental property of biological systems. We previously found that activity in the mouse premotor cortex during motor planning is remarkably robust to large-scale perturbations. Each hemisphere of cortex could independently maintain preparatory activity and support behavior. When one suffered a perturbation, signals from the other hemisphere helped restore correct activity. This previous work suggests a modular organization for robustness across the two hemispheres. However, it is unclear how the two hemispheres coordinate their dynamics and if modularity produces a more robust neural code during normal motor planning. Here, we directly measured interhemispheric interactions using bilateral silicon probe recording in premotor cortex during motor planning. Preparatory activity in each hemisphere was highly independent of the other in some mice. Despite this modularity, preparatory activity was coordinated across hemispheres on single trials, where activity on both hemispheres consistently predicted mice's future movements. This suggests the two hemispheres are weakly coupled. Other mice exhibited lesser degree of modularity, where one hemisphere drove preparatory activity in the other. We found that mice exhibiting modularity were more robust under external unilateral optogenetic perturbations than mice that do not. Remarkably, the degree of modularity also predicted performance variations among individual mice in unperturbed trials. Weakly-coupled modules may enable self-corrections that allow individual modules to overcome internal noise and reduce the probability of making a mistake. Thus, high degree of modularity produced a more robust neural code that enables mice to plan movement accurately under normal and challenged circumstances.

Disclosures: G. Chen: None. **B. Kang:** None. **J.W. Lindsey:** None. **S. Druckmann:** None. **N. Li:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

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Topic: E.04. Voluntary Movements

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Simons Collaboration on the Global Brain

Title: Modulation of superior colliculus biases cortical action representations and behavior

Authors: *A. M. THOMAS, N. LI;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Volitional behaviors require planning prior to execution. Neurons in frontal cortex dynamically encode action plans long before movement onset, yet it remains unclear how these motor representations emerge. Outside of cortex, this preparatory activity has also been detected in motor structures like the superior colliculus. Though evidence implicates both regions in action selection and movement initiation, the nature of their interaction remains poorly understood. We examined cortico-collicular interactions using a delayed response task in mice. Animals used their whiskers to discriminate the position of an object during a sample period. After a delay period (1.3 s), the animals reported their choice via directional licking (left or right). Previous research indicates that the anterior lateral region of motor cortex (ALM) is required to perform the task. Within each hemisphere of ALM, intermingled neurons exhibit preparatory activity that is selective for either contra- or ipsilateral motor responses. A lateral region of the superior colliculus (lSC) has also been suggested to control licking movements (Rossi et al, Nat Neurosci 2016). We found that unilateral activation of lSC evoked contralateral licking, and bilateral inactivation blocked licking altogether. Anatomical tracing experiments revealed that the lSC receives direct input from ipsilateral ALM and projects back to ALM through medio-dorsal and ventral-medial thalamus, forming a loop. Next, the lSC was optogenetically manipulated during different epochs of the delayed-response task. Unilateral inactivation of the lSC during both the delay and response periods (but not the sample period) produced ipsilateral choice biases. Even transient inactivation of lSC during the early delay was sufficient to bias upcoming behavior, with an 800 ms window between the photostimulus offset and go cue, suggesting that the lSC participates in the selection of future movements. Electrophysiological recordings during behavior revealed that the majority of SC neurons showed preparatory and movement-related activity. We next measured the influence of lSC over cortical function by manipulating lSC and recording ALM activity during behavior. Unilateral SC inactivation during the delay period specifically abolished contra-selective representations in ALM, but ipsi-selective representations remained intact, thereby biasing preparatory activity and behavior towards ipsilateral actions. In summary, these results suggest that the SC contributes to the emergence of cortical action representations during motor planning and participates in volitional behavioral control.

Disclosures: **A.M. Thomas:** None. **N. Li:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.12/P6

Topic: E.04. Voluntary Movements

Support: Sackler Brain and Spine Institute Fellowship

Title: Cortical features predict movement dynamics during emergence from anesthesia

Authors: *S. GAO[1,2], V. KRISHNAMURTHY[2], D. P. CALDERON[1];
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Abstract: The electroencephalogram (EEG) is a technique often used to determine the depth of anesthesia. However, the variety of cortical patterns in the EEG associated with the type of anesthetic and concentration have made difficult the implementation of a precise tracking method of depth of anesthesia. Moreover, arousal behavior has been poorly examined during emergence. As a result, current biomarkers lack specificity. We hypothesize that restoring movement during emergence from anesthesia is a dynamic process closely link to changes in cortical activity.
To test this hypothesis, *we* ramped down anesthetic while simultaneously recording local field potentials (LFPs) and movement in mice. We applied a Bayesian Gaussian Mixture model to cortical LFPs and conducted a cross mutual information analysis to predict motor behavior using the clustered cortical states in isoflurane, sevoflurane and a pharmacologically induced arousal model.
The application of cluster analysis to cortical LFPs derived defined cortical states while rodents emerge from the anesthetics. These states served as predictors of intervals in which there is lack of movement, slight movement and generalized movement. The analysis was unable to predict righting reflex, a behavior often used to detect awakening suggesting that cortical involvement is absent in this behavior. Restoring motor behavior is a dynamic process that begins tens of minutes earlier than the righting reflex. Defined cortical states predicted motor behavior in two mechanistically different anesthetics and a pharmacologically induced-arousal model. Understanding the cortical features associated with the dynamics of motor behavior unveils novel biomarkers to accurately track emergence from general anesthesia in rodents and other species.

Disclosures: S. Gao: None. **V. Krishnamurthy:** None. **D.P. Calderon:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.13/P7

Topic: E.04. Voluntary Movements

Title: Distinct activity of pyramidal and fast-spiking neurons in the mouse premotor cortex during a voluntary movement

Authors: *N. C. GIORDANO[1], C. ALIA[2], L. FRUZZETTI[3], A. CATTANEO[4], L. BONINI[5], M. CALEO[6];
[1]CNR - IN / Scuola Normale Superiore, Pisa, Italy; [2]Scuola Normale Superiore - CNR, Pisa, Italy; [3]CNR - IN, Pisa, Italy; [4]Scuola Normale Superiore, Pisa, Italy; [5]Univ. of Parma, Parma, Italy; [6]Neurosci. Institute, C.N.R., Pisa, Italy

Abstract: The premotor cortex is necessary for motor planning. In mice, a putative premotor area controlling voluntary licking has been identified and physiologically mapped in the anterior-lateral motor cortex (ALM). However, the role of distinct physiologically identified ALM neuronal classes in voluntary movement planning and execution is still unknown. To address this issue, we used head-restrained mice trained to lick a reward delivered at random intervals. Mice spontaneously performed either single isolated licks or a burst of consecutive licking events (6-8 Hz), which we categorized, *a posteriori,* into two classes: single (=1 lick) and multiple licks (≥3 consecutive licks). During the task, we extracellularly recorded single unit activity from the ALM using a 16-channels single shank silicon probe. We identified putative pyramidal (PNs) and fast-spiking neurons (FSNs) based on well-established physiological features of their spike waveforms, and then we investigated their functional properties during the licking task. We found that most of the neurons' activity anticipated the licking onset by 100-200 ms. This is consistent with an involvement of the ALM in lick planning. Most of the neurons (about 90%) increased their firing frequency in correspondence with the movement, but suppressive modulations were also observed in a subset of units. For both PNs and FSNs, we found significantly greater discharge during multiple than single licks. Notably, FSNs modulated their activity about 100 ms earlier than the PNs. During multiple vs single licking events, the peak discharge was significantly delayed for both PNs and FSNs. Furthermore, almost all FSNs showed a peak in their response before the beginning of the sequence of licks. The differential timing of activation of PNs and FSNs suggests that inhibitory activity may be relevant for voluntary movement initiation, and FSNs appears to be more directly related to the planning of an entire motor sequence.

Disclosures: **N.C. Giordano:** None. **C. Alia:** None. **L. Fruzzetti:** None. **A. Cattaneo:** None. **L. Bonini:** None. **M. Caleo:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

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Topic: E.04. Voluntary Movements

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Wellcome Trust grant 110131/Z/15/Z
Simons Initiative for the Developing Brain (no official grant no.)

Title: Thalamocortical control of movement initiation

Authors: *J. DACRE[1], M. COLLIGAN[1], J. AMMER[1], V. CHAMOSA-PINO[1], J. SCHIEMANN[1], F. CLAUDI[1], J. M. PAKAN[1], N. L. ROCHEFORT[1,2], C.-C. HUANG[3], A. HANTMAN[3], I. DUGUID[1,2];
[1]Ctr. for Discovery Brain Sci. and Patrick Wild Ctr., [2]Simons Initiative for the Developing Brain, The Univ. of Edinburgh, Edinburgh, United Kingdom; [3]Janelia Res. Campus, Ashburn, VA

Abstract: Motor thalamus serves as a gateway to the cortex, relaying sensorimotor information from subcortical structures to motor-related areas of the cerebral cortex. The cerebellar-recipient region of motor thalamus (MTh_{CB}) is thought to convey the “go” signal for movement execution, yet the underlying neural mechanisms that lead to goal-directed movement initiation remain unresolved. To generate a causal-mechanistic understanding of how movement emerges from the interaction between MTh_{CB} and M1, we trained mice to engage in a goal-directed forelimb manipulandum task. Initial pharmacological inactivation experiments in trained mice revealed forelimb M1 ($M1_{FL}$) output to be essential for limb coordination and task engagement, while MTh_{CB} conveys information necessary for cue-evoked, goal-directed movement initiation. By employing Gradient-index (GRIN) lens-mediated 2-photon population calcium imaging we show that MTh_{CB} output is dominated by a coordinated increase in activity immediately prior to movement initiation. This population-wide neural signature was reliable from trial-to-trial and temporally uncorrelated with respect to cue presentation, consistent with a feedforward movement initiation signal. To investigate how MTh_{CB} input shapes cortical output, we performed whole-cell patch-clamp recordings from L5B projection neurons in $M1_{FL}$. Individual L5B neurons exhibited consistent membrane potential trajectory changes across trials spanning a continuum from hyperpolarised to depolarised, with the onset dynamics of these subthreshold signatures reliably following that of the recorded MTh population. To provide a causal link between MTh activity, motor cortical output and movement initiation, we employed a dual optogenetic stimulation strategy employing either direct stimulation of motor thalamic neurons or motor thalamocortical axon terminals in $M1_{FL}$ in the absence of an auditory cue. Both manipulation strategies resulted in recapitulated forelimb push movements in 30 - 50% of trials,

driven by L5B pyramidal neuron V_m trajectories similar in magnitude and direction to cue-evoked trials. Importantly, light-evoked forelimb push movements were context-dependent. Together, our findings provide the first causal-mechanistic description of how MTh_{CB} interacts with primary motor cortex to initiate goal-directed forelimb movements.

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Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.15/P9

Topic: E.04. Voluntary Movements

Support: ERC StG 678790 NEWRON

Title: Synaptic and cellular basis for prefrontal anticipation of motor behavior

Authors: C. ZHANG, M. ALLEGRA, F. KOUKOULI, U. MASKOS, J.-P. CHANGEUX, *C. SCHMIDT-HIEBER;
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Abstract: Neuronal activity in the prefrontal cortex (PFC) in rodents is associated with voluntary motor behavior. To drive motor action, PFC neurons need to integrate information about the external world and internal states. However, how synaptic inputs to these neurons are integrated and modulated during anticipation of voluntary movement remains unclear. Here we address this question by performing *in vivo* whole-cell patch-clamp recordings and 2-photon imaging from PFC neurons in awake mice during resting and voluntary movement on a treadmill. We find that PFC principal neurons show large membrane potential fluctuations during resting periods (variance 28 ± 3 mV^2, n=26) that decrease in amplitude before and during spontaneous running periods (variance 16 ± 4 mV^2, n=26). In addition, action potential firing frequency increases before the onset of spontaneous running in most PFC neurons, but then remains low (0.3 ± 0.2 Hz, n=26) throughout the running period. *In vivo* two-photon Ca^{2+} imaging from superficial layers of PFC confirms this anticipatory activity signature for a subpopulation of PFC principal neurons. Both pharmacological blockade of nicotinic acetylcholine receptors and chemogenetic inhibition of parvalbumin-positive GABAergic interneurons can affect membrane potential dynamics and spike firing before and during voluntary movement. Together, our results provide insight into how cholinergic modulation of GABAergic inputs to the PFC exerts a critical influence on neuronal activity during anticipation

of motor behavior, suggesting that it may play a role in decision making during anticipation of movement.

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Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

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Program #/Poster #: 494.16/P10

Topic: E.04. Voluntary Movements

Support: NSERC
FRQS

Title: A motivation signal in motor cortex for high-stake actions

Authors: *M. ELBAZ, S. SUBRAMANIAM, Q. LEJEUNE, C. ETHIER;
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Abstract: In both rodents and primates, the motor cortex is involved in controlling the execution of skilled movements. Yet, during skilled movements, movement-related activity in motor cortex does not fully account for trial-to-trial neuronal variability. Both upstream (e.g., cognitive) and downstream (e.g., feedback) components may thus modulate motor cortical activity during skilled execution.
Motivation might be one of the cognitive components modulating motor cortical activity. Indeed, skilled movements require attention, a cognitive effort. As the stake of the action increases, a greater effort to maintain an optimal attention may be engaged, resulting in a greater need for motivation. In this scenario, skilled movements' proper execution would rely on finely adjusted motivation and depend on the anticipated stake of the action.
To test whether the motor cortex encodes motivation during skilled movements, we designed a behavioral task in which rats are trained to pull on a lever and maintain a pulling force above a specified target level, for a predetermined duration, in order to obtain either zero, one, or five food pellets. One of three tones, indicating to the animals the amount of reward to expect, is played at the onset of each trial when the rats make initial contact with the lever.
Remarkably, up to 500ms before rats initiate a trial, i.e. before they know the stake of the upcoming trial, motor cortical preparatory activity already contains information about their motivation. Indeed, a particular preparatory activity is required for the rats to succeed in high-stake trials, although the required motor action to successfully complete a trial is the same, whatever its stake.
Our results provide two novel observations: 1- motor cortical activity is modulated by expected

reward value during movement, and 2- the importance of an adequate preparatory state for the success of a skilled motor action varies with respect to its expected reward value.

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Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

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Program #/Poster #: 494.17/P11

Topic: E.04. Voluntary Movements

Support: Whitehall Foundation
Kauffman Foundation

Title: Causal dissection of cortical-striatal interactions governing the neural circuit control of reaching

Authors: ***M. A. NICHOLAS**, P. BELSEY, E. A. YTTRI;
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Abstract: Motor cortex and the basal ganglia work together to plan movements, potentially through the generation of motor plans and control of kinematic parameters respectively. This hypothesis, as well as other contrasting notions, have clear and testable predictions about the contribution of motor cortex to striatal dynamics and animal behavior. However little is known of basal ganglia dynamics and goal-oriented behavior change in the absence of input of motor commands from motor cortex during recovery from surgical ablation.
First we sought to study movement kinetics during goal directed behavior before and immediately after ablation of the caudal forelimb area (CFA). Age and sex-matched adult mice (n=6) were trained to perform a self-paced bimanual forelimb movement task to gain a fluid reward and upon reaching expert performance, mice received bilateral aspiration lesions of CFA. The first task implemented non-dexterous reaching and did not require fine-movement control or timing, but rather the joystick movement beyond an amplitude threshold. Directly following recovery from anesthesia, mice were run on the above task and continuously each day following lesion until recovery. We found that movement kinetics are severely impaired immediately following ablation and begin to recover towards baseline performance following 6-8 days.
A second cohort of mice were trained in a reaction time task, wherein the reach was required to wait for a go-cue occurring at a random point in time. Following lesion, again we found a severe impairment of movement kinetics that returned over time. Reaction time was found to drastically increase and then return to pre-ablation levels. Population activity within the striatum demonstrated a similar trend of decreasing and returning to pre-ablation levels comparable to the movement kinetics recovery time. However, neural tuning to movement onset and kinematics

was permanently lost.
Finally, the locomotor abilities of all mice were evaluated before lesion and every day following to study potential effects of surgical ablation of motor cortex. We found the locomotion was largely intact, but that the when faced with a decision the animal paused in place for tens of seconds.
Results of the above studies help to understand how the brain can control for movement dynamics during goal directed behaviors as well as during recovery from cortical damage. Decisions related to movement initiation and control arise from multiple brain areas and this study aims to use highly quantifiable movement kinetics, neural activity and non-dexterous behavioral tasks to elucidate the roles of crucial nodes of this networks both before and following surgical ablation.

Disclosures: **M.A. Nicholas:** None. **P. Belsey:** None. **E.A. Yttri:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.18/P12

Topic: E.04. Voluntary Movements

Title: Flexible routing of bimanual forelimb movements by dual descending pathways of the motor cortex

Authors: *J. PARK, J. W. PHILLIPS, A. HANTMAN, J. T. DUDMAN;
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Abstract: An action is defined by the outcome achieved rather than specific movements executed. Actions can maintain a robust independence relative to specific effectors. This implies that actions comprise both abstract representations and flexible realizations thereof as concrete movements. One common example of this flexibility is the ability to make coordinated movements of one or both limbs. Such flexibility is thought to be mediated by descending neocortical control. In line with this, sustained activation of motor cortical regions can produce both uni- and bimanual movements. Moreover, a putative cortical substrate for bilaterally coordinated control and unilateral control are the intratelencephalic (IT) and pyramidal tract (PT) classes of deep layer projection neurons. However, little is known about the cortical control of bimanual actions. The majority of work has focused on single limb movements of reaching to a target, grabbing and manipulating an object. In general, these studies found modest differences between IT and PT neural correlates of movement. To address these issues, we trained mice to make bimanual movements of a joystick past varying thresholds - a quantitative, goal-directed task that is sensitive to acute inactivation of motor cortex. Harnessing dense sampling across depths with Neuropixels recordings we found that movement-related activity dimensions were

not evenly weighted across depths. Optotagging suggested that this depth difference indeed reflected a difference in cell-types. This observation was confirmed with cell-type specific calcium imaging. In sum, we discovered a clear dissociation between IT and PT neural correlates during bimanual forelimb movements. IT neurons exhibited dramatically stronger modulation than PT neurons. However, the relative magnitude of IT or PT activity modulation was not perfectly aligned to a key movement-related dimension of population activity suggesting that neither population alone was obligate for motor execution. In line with this, cell-type specific perturbation produced large, distributed changes in neural activity. Surprisingly, despite these changes in many individual neurons, some modes of population dynamics remained unaltered consistent with little change in movement quality. Thus, large mean changes in the activity of IT and PT neurons were primarily confined to a 'movement-null' dimension of motor cortical population activity. Taken together, these provide a compelling model for the flexible routing of cortical output activity with conserved motor kinematics. We suggest that this may be a key element to the flexible, effector independent, control of purposive action.

Disclosures: **J. Park:** None. **J.W. Phillips:** None. **A. Hantman:** None. **J.T. Dudman:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.19/P13

Topic: E.04. Voluntary Movements

Support: NSF NCS #1835390
University of Chicago

Title: Calcium imaging reveals neurons with complex activity patterns in mouse motor cortex during a reach-to-water task

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Abstract: Electrophysiology in non-human primates has shown that motor cortex generates complex, time-varying activity patterns during reaching and grasping. We wish to understand whether motor cortex dynamics are similar in the mouse. Two-photon calcium imaging has enabled recording the activity of large numbers of neurons in head-fixed mice performing well-controlled forelimb motor tasks. Examining neural activity during reaching in mice provides the possibility of comparing cortical dynamics during these behaviors across species, identifying interspecies commonalities and differences. Using a simplified version of an established reach-to-water task with two targets (Galinanes et al. 2018), we simultaneously recorded activity of 1189-1492 neurons in layer 2/3 of the caudal forelimb area (CFA) in transgenic GCaMP6s and

virus-injected GCaMP6f mice as they performed reaches cued by sound. Preliminary data show that a substantial fraction of neurons are significantly modulated by this task; 56-78% of cells were significantly modulated over time or across condition. Interestingly, many of these modulated neurons nonetheless had low estimated firing rates: ~50% of modulated neurons showed firing rates <1.5 events/s over the full course of the reaching behavior. With sufficient trial counts, a subset of neurons were identified displaying complex time-varying patterns beyond the featureless "bump" of activity often reported in mouse motor behaviors. In both GCaMP6s and GCaMP6f animals, fine temporal features were present in ~10% of cells, including those with low firing rates. This was corroborated by cross-validated Principal Component Analysis across neurons which revealed a dimensionality in the range of 2-5. The presence of complex single-neuron firing rate patterns even in low-firing-rate cells suggests that cortical dynamics during mouse reaching behaviors may be more distributed than previously thought, with pattern generation involving even low-firing neurons that are often ignored.

Disclosures: H.A. Grier: None. **M.T. Kaufman:** None.

Poster

494. Cortical Planning and Execution: Neurophysiology in Rodents and Others I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 494.20/P14

Topic: E.04. Voluntary Movements

Support: NIH MH104716
NSF NCS 1835268

Title: Role of rat secondary motor cortex in complex movements and decision making

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Abstract: Modern Brain Machine Interfaces (BMIs) use increasingly more recording channels to facilitate the simultaneous access to large numbers of neurons. These systems require heavy computational resources and offline signal processing. In order to develop a portable and autonomous BMI, suitable for brain controlled robotic prosthesis, it is necessary to reduce the computational requirements of these systems. One way to address this issue is to investigate motor coding in different brain areas, in which neuronal populations use different strategies to encode or drive actions. The secondary motor cortex has been found to be involved in several cognitive / high-order functions, although it is not clear how neural representations of these higher-order functions are related to the details of complex movement encoding. One possible

route to developing optimized, efficient BMI decoding strategies is to focus on this area. Thus the goal of the current project is to determine the extent to which neuron ensemble activity in rodent secondary motor cortex encodes high-level goals and decisions vs. specific mechanics of motor commands.
To address this issue, we trained 4 male fluid-restricted Long-Evans rats to perform a 2-alternative forced choice (2AFC) task on an automated T-maze. During the task, animals were presented with two different cues (1 and 8 kHz tones) which specified the need to choose either the left or right side (counterbalanced across animals) to receive reward (20 ul water). Following correct or incorrect choices, rats are required to return to the starting point (through returning arms) to start a new trial. Sessions consisted in between 150 and 350 trials. All animals reached 80% correct trials after 5-10 sessions.
After the criterion was met, rats were implanted with a custom 16 tetrode chronic drive in secondary motor cortex (AP +2 to +3, ML +0.5 to 1.5). Tetrodes were initially implanted at 0.5 mm ventral from the surface of the brain and driven down to 2.5 mm in 80 um steps after each recording session. Single neuron and local field activity is currently being recorded using the Open-Ephys acquisition system and Intan headstages.
During task performance, rats are filmed with two cameras mounted on the ceiling, and detailed behavior tracking is performed offline with DeepLabCut software. To date we have recorded a small number of neurons in secondary motor cortex during these behaviors and have demonstrated the ability of DeepLabCut to track rat behavior on our task. These preliminary results support feasibility of our ongoing studies in which neural correlates of 2AFC decisions will be contrasted with the specific motor plans required to enact these decisions.

Disclosures: **A. Burman:** None. **E.M. Vazey:** None. **D.E. Moorman:** None.

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.01/P15

Topic: E.05. Brain-Machine Interface

Support: National Institute of Health Grant R01NS106094
Office of Naval Research Grant 2002761143
National Science Foundation Graduate Research Fellowship Program

Title: The rate of neuroprosthetic learning is invariant to initial levels of closed-loop decoder adaptation

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Abstract: Previous work has shown that the neural adaptation facilitates the consolidation of skillful neuroprosthetic control. Meanwhile, closed-loop decoder adaptation (CLDA) algorithms can reliably improve macaque monkeys' initial behavioral performance without hindering the beneficial neural adaptation, such as the formation of a stable neuroprosthetic tuning map. However, it is not fully understood how the formation of these maps and the consolidation of neural activity patterns are affected by different initial levels of decoder adaptation. Here we investigated how neural patterns changed while macaque monkeys learned to control a brain-machine interface (BMI), via chronically implanted electrode arrays in motor cortex, using decoders with varying levels of initial adaptation. Our results show that the rate of improvement in BMI control is invariant to the initial levels of decoder adaptation. Furthermore, this behavioral improvement is highly correlated with the formation of the ensemble activity pattern. This suggests neural mechanisms underlying neuroprosthetic learning that are independent of decoder adaptation levels.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

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Program #/Poster #: 495.02/P16

Topic: E.05. Brain-Machine Interface

Support: NIH Grant HD087955

Title: Closed loop BCI decoder optimization in a tetraplegic subject with a chronic ECoG implant

Authors: *D. B. SILVERSMITH[1], R. ABIRI[1], N. HARDY[1], E. F. CHANG[2], K. GANGULY[1]; [1]Neurol., [2]Neurosurg., UCSF, San Francisco, CA

Abstract: Brain-Computer Interfaces (BCIs) promise to assist individuals with severe motor impairments. A great deal of progress in decoder optimization and rapid calibration for BCIs has been made over the last decade; in particular, closed loop decoder adaptation (CLDA) algorithms are commonly used to achieve quality BCI performance with minimal training data. However, these algorithms have primarily been developed and tested using spike-based neural features from monkeys with intact motor systems. Comparable performance in human assistive BCIs has remained elusive.
Here, we tested the capacity for chronic electrocorticography (ECoG) implants to support BCI

control. Generally, ECoG implants have been proposed as a compromise with high enough spatial resolution while causing less tissue damage than more invasive, spike-based implants. Recent work by Wang and colleagues has demonstrated the potential for short-term ECoG implants (i.e. < 30 days) to support BCI control in human subjects with motor impairments. We tested and further developed CLDA algorithms in a human tetraplegic subject with a chronic ECoG interface. More specifically, we implanted a 128-channel ECoG grid over the left motor and somatosensory cortices of a subject with bilateral pontine strokes resulting in tetraplegia. We then developed a real-time system to acquire signals, process and detect neural features, and decode motor intention using a Velocity Kalman Filter decoder. We then calibrated our decoders for each experiment using CLDA algorithms to achieve fast, stable control and evaluated decoder performance on a Center-Out task. We have specifically tested ECoG BCI performance while systemically varying neural features and varying system parameters, e.g. changing decoding timescales and incorporating methods to compensate for signal non-stationarities. Preliminary results suggest that incorporating a range of low to high frequency neural features, longer decoding timescales and enabling continuous CLDA led to the best performance. Our results provide further support for the possible use of an ECoG-based implant for neuroprosthetic control.

Disclosures: D.B. Silversmith: None. **R. Abiri:** None. **N. Hardy:** None. **E.F. Chang:** None. **K. Ganguly:** None.

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

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Program #/Poster #: 495.03/P17

Topic: E.05. Brain-Machine Interface

Support: NIH R01EY024678 (SK)
Curci Foundation

Title: Use of optical brain-computer interface to identify neural strategies underlying new skill acquisition and performance following extended practice

Authors: *B. B. JEON[1], S. M. CHASE[1], S. J. KUHLMAN[2];
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Abstract: The circuit basis by which new skills are acquired and executed is ill-defined. This is in part because learning is a complex, distributed process involving neurons from multiple brain areas, as well as multiple cortical cell types. Brain computer interfaces (BCI) can circumvent this issue by creating a causal relationship between the activity of a defined set of neurons and a

rewarded outcome. We developed hardware to read out the real-time neural activity of ensembles of individual neurons in awake, behaving mice using 2-photon calcium imaging. We then used this system to address the question: once adopted, is a successful strategy recalled repeatedly in subsequent sessions? Four mice were successfully trained to control a BCI device, using the same ensemble of six cortical excitatory neurons from layer 2/3 over the course of multiple imaging sessions lasting approximately one to two weeks. In this task, the summed activity of three randomly selected neurons, referred to as 'direct positive' neurons, is used to drive an auditory cursor to a target threshold; an additional 3 'direct negative' neurons are randomly selected and their combined activity is subtracted from the drive to threshold to prevent the subject from simply increasing the activity of all neurons within the local circuit. When the target is reached, a water reward is available for the mouse to collect. Mice performed up to 600 trials per session, and we quantified performance as the percentage of trials in which the target was successfully reached within the session. A trial is scored as unsuccessful if the target is not reached within 10 seconds of the trial start. There are three broad categories of strategy by which subjects could gain control of the device. First, they could increase the frequency by which the three 'direct positive' neurons coordinate their activity to reach the target. Second, they could decrease the activity of 'direct negative' neurons. Third, they could drive one of the 'direct positive' neurons to cross the target threshold.
In all cases (each of the 4 mice), subjects incorporated the strategy of increasing the drive of one 'direct positive' neuron to cross the target threshold. Further analysis revealed that within a given session all mice used multiple strategies, and once a strategy was adopted, it was not necessarily repeated in subsequent sessions. These results indicate that during practice of a newly acquired skill, neural circuits exhibit volitional flexibility.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.04/P18

Topic: E.05. Brain-Machine Interface

Support: R01 NS110423

Title: Dynamical influence of premotor and primary motor cortex during movement

Authors: *R. A. D'ALEO[1], A. G. ROUSE[2], M. H. SCHIEBER[3], S. V. SARMA[4];
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Abstract: Investigating what neurons in different motor regions encode during movement provides insight into the complex sensorimotor control system. While there are anatomical distinctions between premotor cortex (PM) and primary motor cortex (M1) attributed to their upstream and downstream pathways and cytoarchitecture, their functional distinction within the motor pathway is less clear as they have largely been studied independently using static correlations between kinematics and neural activity. To disentangle PM and M1 during movement, experimental paradigms have relied on delay tasks which have led to the interpretation that PM is involved in preparation of movement and M1 is involved in execution of movement. However, these analysis methods and experimental paradigms have limited ability to interpret dynamical interactions and influence across cortical regions. A recent approach to studying neuronal activity during movement is to construct a dynamical systems model (DSM), wherein cortical activity is perceived as a trajectory through a neural state-space, which in turn generates a movement in physical space. This approach allows for the populations to influence each other in a dynamical manner, which in turn generate movement. To date, applications of DSM have relied on delay paradigms in which the movement is decomposed into preparation and execution, characterizing activity in single regions and over brief time periods during which no abrupt events (e.g. movement onset) or stimuli (e.g. visual cue) occur. To capture long time periods, a different DSM is constructed in each time period that modulate with different external events. Here, we expand the DSM framework to allow for a *single* model to characterize neural dynamics (i) over the entire non-delay movement task (ii) during which multiple events occur and (iii) between multiple brain regions. The events are modeled as exogenous inputs driving the activity in PM and M1, whose firing rates are in general coupled and evolve dynamically to generate kinematic output. We apply our general DSM approach to neuronal data captured in two nonhuman primates executing a reach-to-grasp task and demonstrate the model's ability to reconstruct population activity in *both* PM and M1 simultaneously in addition to kinematic trajectories. Evaluation of the DSM solution allows us to uncover functional distinctions between PM and M1 through the influence of each cortical population on the neural and kinematic state throughout an arm reaching movement.

Disclosures: **R.A. D'Aleo:** None. **A.G. Rouse:** None. **M.H. Schieber:** None. **S.V. Sarma:** None.

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

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Topic: E.05. Brain-Machine Interface

Support: Italian National Institute for Insurance against Accidents at Work (INAIL) funding

ERC Starting Grant 759998

Title: Awakening proprioception in neuroprostheses: Modeling of muscle spindles transducers

Authors: *A. CIMOLATO[1,2,3], M. LAFFRANCHI[2], E. DE MOMI[1], S. RASPOPOVIC[3]; [1]Dept. of Electronics, Information Sci. and Bioengineering, Politecnico Di Milano, Milano, Italy; [2]Rehab Technologies, Inst. Italiano di Tecnologia, Genova, Italy; [3]Dept. of Hlth. Sci. and Technol., ETH Zürich, Zuerich Eth-Zentrum, Switzerland

Abstract: Proprioception, in specific kinesthesia sensation is essential in legged motor control since it provides kinematic information about the state of the body segments. Muscle spindles receptors along intrafusal muscles translate their stretch into nervous activity through two distinct type of afferent fibers. Human modelization and validation has always been a major issue due to the impossibility of simultaneous fiber elongation and microneurography recordings. Objective of this work is to propose a computational model able to predict neural firing activity from muscle spindles afferent fibers during human legged locomotion. Musculoskeletal modeling is used in order to simulate in silico the lower limb motion and estimate the interested muscles' kinematics. This particular step allows investigation on human data of previously proposed muscle spindle transducer model, validated only on animals' recordings. Microneurography of muscle spindles afferent fibers and task related joint trajectories from previous studies on humans are used for model reparametrization and validation. Sequential combination of musculoskeletal modeling and the proposed muscle spindles transducer model are planned to be employed in the designing of a bidirectional lower limb neuroprosthesis. Predicted activity will be used through invasive neural stimulation to restore real-time proprioceptive feedback during voluntary prosthetic joint movements.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.06/P20

Topic: E.05. Brain-Machine Interface

Support: UCSF Program for Breakthrough Biomedical Research

Title: Multiphoton imaging in alert mouse visual cortex reveals sparse, distributed activation of neurons by electrical stimulation

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Abstract: Electrical stimulation is a highly-effective, temporally-precise technique to evoke neural activity in the brain, and is critically important in research and for clinical applications. Understanding the strength, time-course, and spatial spread of neural activation elicited by electrical stimulation in awake, behaving animals is therefore of great interest. To do so, we imaged visual cortex of chronically-implanted transgenic mice using 2-photon fluorescence calcium imaging to measure responses of inhibitory and excitatory neurons evoked by electrical stimulation. GAD-CRE Ai14 mice, which labeled inhibitory neurons with tdTomato, were injected with an AAV 2/1 GCaMP6s virus. A plate for head fixation and a single stimulating microelectrode were implanted and covered by a three mm glass cranial window centered over the electrode tip. After allowing three to four weeks for viral expression, the mouse head was fixed while it stood or ran on a styrofoam ball floating on air. Electrical stimuli consisted of a train of twenty-five biphasic pulses delivered at 250 Hz with a range current amplitudes (1, 5, 10, 15, 20, 25, 30, 40, and 50 microamps). Ten repetitions of each stimulus were presented at each current amplitude, delivered in pseudo-random order once every ten seconds. The number of neurons significantly activated by stimulation grew with the amplitude of stimulation current; however, recruitment of neurons was sparse and distributed across the imaging field — many neurons close to the electrode tip were never activated, even at the highest stimulation amplitudes. Nevertheless, the fraction of neurons activated by stimulation fell with distance from the electrode tip, as did the magnitude of evoked responses. Finally, we found that the pattern of activation evoked by electrical stimulation was similar for excitatory and inhibitory neurons, and was stable over the change in cortical state induced by locomotion.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

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Program #/Poster #: 495.07/P21

Topic: E.05. Brain-Machine Interface

Support: a grant to CABMC(Control of Animal Brain using MEMS Chip) funded by Defense Acquisition Program Administration(UD140069ID)

Title: Midbrain nucleus in pigeon generates locomotion elicited by electrical stimulation

Authors: *J. JANG[1], Y. JUNG[1], C. BAEK[2], S. PARK[3], S. SHIM[2], K. SEO[3], J.-M. SEO[2], S. KIM[2], Y.-K. SONG[1];
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Abstract: The research topic of controlling animal behavior through the locomotion system is a fundamental study for the field of robo-animals. Among them, the pigeons have the advantage of having a wide field of view that cannot be seen by people and flying away extremely long distances without being disturbed. However, brain-machine- interface(BMI) technology that implements the aviation capability of the bird still at an elementary level, the need for research related functional aviation brain mapping is increasing. Although the anatomy of the central nervous system of the pigeon has been well-established, it remains unknown about the correlation of what extent structure with function of the flight-related motor nucleus in the brain. In particular, the avian study for functional brain mapping is much uncertain compared to primates, the fundamental study on the motor mechanism of the avian flight is essential. Therefore, in this study, we explore the specific motor areas of the pigeon brain, electrically stimulate to elicit motor or flight behavioral responses and visually evaluate by using movement tracking.
Stereotactic insertion of four monopolar depth electrode(0.203mm) were targeted to pigeon(*Columba livia*, n=9) midbrain. Three locomotion-associated midbrain nuclei containing FRM(Formatio reticularis medialis mesencephalic), ICo(Ventral part of Nucleus intercollicularis), and PAG(Periaqueductal gray) were investigated to elicit flying and walking behaviors. We found that pigeon's body movement including turning, flapping flight, and walking was successfully generated while FRM, ICo, and PAG were electrically stimulated, respectively. The overall electrical current to stimulate these nuclei was of 1mA intensity and 200μs duration.
In this study, we have investigated the behavioral function of particular midbrain nuclei and demonstrated intended motor actions of axial turning, flapping flight and walking. We also have established techniques to implant electrodes into the pigeon brain more accurately and consistently via a stereotaxic frame with a bird-specific adapter. Although our research executed with a wired stimulator in a closed space, future studies using the wireless system could provide more meaningful results if flight experiments are conducted in an open-field. In addition, we expect to induce natural movement of takeoff, landing and flight through simultaneous stimulation of multiple nuclei.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

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Program #/Poster #: 495.08/P22

Topic: E.05. Brain-Machine Interface

Support: Hartwell Foundation Grant
Duke Neurosurgery Grant

Title: Behavioral assessment of sensory percepts induced by dorsal thoracic epidural spinal cord stimulation in primates

Authors: *A. P. YADAV[1], M. O. KRUCOFF[1], M. A. LEBEDEV[1], M. ABD-EL-BARR[2], M. A. NICOLELIS[1];
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Abstract: Lack of somatosensory feedback is a major obstacle to optimally integrating neural prostheses into an individual's body schema. Electrical stimulation of the somatosensory cortex and thalamic nuclei have been proposed to generate sensory percepts in individuals with loss of sensorimotor function; however, these targets require open intradural cranial surgery and accurate targeting of tiny brain structures. It is plausible that alternative target structures along the somatosensory pathway might be capable of encoding meaningful sensory percepts induced by electrical stimulation in a less invasive and more readily clinically translatable fashion. Previously, our group demonstrated that stimulation of the dorsal surface of the spinal cord in rats can be used to transmit sensory information to the brain, and that rats learn to discriminate temporally varying patterns of dorsal column stimulation. In the present study, we generated sensory percepts using percutaneous leads implanted on the dorsal surface of the spinal cord in 3 rhesus macaques, using a routine procedure that is performed in over 50,000 human patients annually and is FDA-approved for certain pain-control indications. Three monkeys were trained to move a joystick-controlled cursor into one of two visual targets. After basic training on the joystick task, they were implanted with epidural percutaneous leads on the dorsal surface of the spinal cord, and externalized leads connected to a custom external pulse generator. Monkeys had to hold a cursor inside a center target during a brief preparatory period while electrical stimulation was presented. Using a two-alternative forced choice task, monkeys were trained to detect artificial stimuli generated by electrical signals delivered at the lead contacts in a charge-balanced bipolar biphasic manner. Using psychometric analysis, we then studied the behavioral sensitivity to detection of sensory percepts at various stimulation parameters such as frequency, pulse width, and duration. We observed that the current threshold for detection of sensory percepts significantly decreased with an increase in frequency, or pulse-width, or duration of stimulation. We also showed that monkeys were able to discriminate between two stimuli that

varied in stimulation frequency as well as those that varied in spatial location. Our results suggest that thoracic epidural spinal cord stimulation can be used to provide valuable information from a prosthetic device back to the central nervous system through a non-visual route, and that the relationship between sensory percepts and stimulation parameters can be explored to create discriminable percepts.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

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Program #/Poster #: 495.09/P23

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant NS110605

Title: Population level analysis of the correlations between spinal interneuron and motoneuron firing during reflexive motor activity in the spinalized and spinal intact decerebrate cat

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Abstract: Spinal alpha motoneurons receive most of their synaptic input through spinal interneurons, yet population level patterns of activity between spinal interneurons and motoneurons have not been widely investigated. We present an approach to record large numbers (>30-50 per trial) of spinal interneurons and motor units in order to better quantify how interneurons influence the firing of motoneurons. The experiments were performed on spinalized or spinal intact decerebrate cats. Lumbar spinal cord recording sites were exposed via laminectomy. The right hind limb was secured to a frame and two ankle extensors (soleus and medial gastrocnemius (MG)) were exposed and their tendons separated. In the spinal intact cats, cuff electrodes were placed on the ipsilateral sural nerve and contralateral common peroneal (CP) and tibial nerves. Two 64-channel microelectrode arrays were inserted into the L3 and L6/L7 spinal segments just medial to the ipsilateral dorsal root entry zone to record throughout the intermediate zone of the spinal gray. 64-channel electrode arrays were placed onto the muscle belly of the right MG and/or soleus. Reflexive motor activity was evoked through tendon vibration (~100Hz) or stimulation of the CP, tibial or sural nerves. Neural and EMG units were decomposed and the spike times of both types of units correlated using generalized-linear-model (GLM) analysis methods. Motor units were generally quiescent at rest but showed a robust

increased discharge rate in response to vibratory or nerve stimuli. In contrast, a number of interneurons were active at rest with some demonstrating significant increases in average discharge rate in response to vibratory or nerve stimuli. For vibratory stimuli, motoneurons demonstrated interspike intervals (ISI) tied to the fundamental or harmonics of the vibration frequency, while this was not observed for most interneurons. This differing pattern of activation is consistent with the direct monosynaptic projections from the muscle spindle onto the homonymous motor pool; highly punctuated ISI histograms are frequently observed at the level of the motoneurons, but relatively infrequently across spinal interneurons. GLM analysis showed a number of significant interactions between interneurons and individual motor units that were not observed in some of our prior work looking at interneuronal firing and intramuscular EMGs. The ability to collect these spike train data simultaneously and in large numbers is necessary to better quantify the synaptic input from spinal interneurons to spinal alpha motoneurons under a variety of reflexive, pharmacological, and surgical conditions.

Disclosures: M.A. Lemay: None. **M.A. Gallo:** None. **S. Shankar:** None. **A.J. Krupka:** None. **C.K. Thompson:** None.

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

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Program #/Poster #: 495.10/P24

Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant R01 NS098509

Title: The motor command to a single motor pool during different modes of activation

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Abstract: Muscle force and movement are generated through the graded activation of spinal motoneurons. It remains unclear how the CNS regulates the activation of spinal motoneurons. There are two commonly debated theories; the motor command encodes for kinematics or kinetics. Here, we record the discharge of single motor units from the biceps during two isometric tasks, elbow flexion and forearm supination, at similar levels of intensity to quantify the synaptic input to and intrinsic excitability of human spinal motoneurons during these modes of activation. High-density surface electromyography of the short head of the biceps brachii was recorded from 11 neurologically intact participants while they performed low-level, isometric, flexion or supination contractions. These contractions were guided with visual feedback and consisted of either steady holds or time-varying efforts. These data were decomposed into their

underlying motor unit action potentials using a well-validated algorithm. The synaptic input to the motoneuron was estimated using intramuscular coherence whereas the excitability of spinal motoneurons was quantified using hysteresis between appropriate motor unit pairs (delta-f). Intramuscular coherence in the 7-12 Hz band was greater in 10/11 individuals during supination than in flexion. No differences were observed in other frequency bands. No difference was observed in the excitability of spinal MNs between modes of activation. These data suggest the synaptic drive to biceps motoneurons may be different during different modes of activation, while the excitability of the motor pool remains invariant. These alterations in common synaptic drive suggest the motor command to the biceps motor pool contains information regarding the limb movement.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.11/P25

Topic: E.09. Motor Neurons and Muscle

Title: Motor unit activation underlying upper limb reflexes to a mechanical displacement

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Abstract: Over fifty years of research has examined feedback corrections to unexpected perturbations to our limbs or body. A common limitation of this work is examining the compound electrical activity (net EMG) rather than the underlying action potentials of isolated motor units. A handful of studies obtained this information through the time-consuming approach of indwelling electrodes. Here we describe preliminary data using high-density surface EMG electrodes to non-invasively identify dozens of concurrently active motor units. Six healthy individuals (23-47 yr) were seated with their right arm encased by a robotic exoskeleton while a high-density array electrodes was placed over their elbow flexor (brachioradialis) and elbow extensor (triceps lateral). For partial validation, fine-wire electrodes were sometimes inserted into the target muscle. Subjects performed a simple postural task: maintaining their hand within a 1 cm target against a constant flexion or extension torque at the elbow followed by a randomly timed pulse of elbow torque (100ms) which stretched or shortened the contracting muscle. Six blocks of 20 trials were collected. The resulting surface signal was decomposed into corresponding motor unit discharge times using an automated decomposition algorithm, whereas intramuscular EMG was decomposed using a semi-automated tool. Muscle activity and motor

unit discharge was assessed with the conventional approach of peristimulus time histograms (PSTHs). This yielded a high rate of agreement between the array and fine wire decomposition. PSTHs on net EMG and motor unit discharge also demonstrated a high correspondence in the series of bursts termed the short-latency (20-50ms) and long-latency (50-100 ms) reflex. Peristimulus frequencygrams (PSFs) were also constructed from motor unit discharge times and demonstrate high levels of consistency across muscles, perturbations, and subjects. Moreover, there was a notable difference in the PSFs during the short- and long-latency epochs: motor unit activity in the short-latency epoch expressed little change in firing frequency whereas motor unit activity in the long-latency epoch expressed a large sustained increase in firing frequency. Our preliminary results demonstrate the ability to decompose multiple motor units in upper limb muscles during mechanical perturbations and reveal patterns that could not be observed in the net EMG. Different PSFs between the short and long latency reflex epoch likely reflects different their afferent signals and central circuits and will require realistic sensori-motor models for their proper interpretation.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

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Program #/Poster #: 495.12/P26

Topic: E.09. Motor Neurons and Muscle

Support: National Natural Science Foundation of China (Y73BN11171)
National Key R&D Program of China (Y72FN91171)

Title: Distinct contributions of mesencephalic locomotor regions in locomotion control

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Abstract: Movement control is important for animals to survive in the changing world. Based on the internal and external needs, the individual should respond to initiate, maintain, or terminate its locomotion. Long before in 1970s, the mesencephalic locomotion region (MLR) has been identified as a key region to modulate locomotion by electric stimuli, eliciting locomotion in the dorsal region and stopping locomotion in the ventral part. Recently, with optogenetics methods and transgene mice, researcher have figured out distinct contributions of MLR to locomotion at cell-type-specific level. The general idea is that vGluT2 neurons initiate and speed up locomotion, whereas GABA neurons slow down and terminate locomotion. However, there are

still more questions on how different inputs of MLR precisely modulate locomotion, and how the sub-populations of MLR execute our behavior. In the present study, by using rats in our studies, we tried to make more subdivision of MLR and examined the fucnction of those sub-regions on locomotion. In our preliminary results, we found that rats' locomotion was halted or speeded up by photostimulation activation of neurons from rostral to caudal of MLR, respectively. By tracing the sources of neural inputs into each sub-region by CTB-647, we found that the rostral of MLR receives more projections from Central of Amygdala (CeA) and Substantia nigra pars reticulata (SNr), while the caudal of MLR more from superior colliculus (SC) and Periaqueductal gray (PAG). In our future work, we will try to figure out how those sub-population neurons receiving different inputs regulate locomotion in MLR. Since locomotion disorder is associated with some disease, such as Parkinson's Disease and Huntington's disease, the results of our studies will be helpful to understanding mechanism of those disorders and the invention of new treatments.

Disclosures: Y. Huang: None. **Z. Wang:** None.

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.13/P27

Topic: E.09. Motor Neurons and Muscle

Title: Characteristics of the pubococcygeus muscle motoneurons reflex activity in the male rat

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Abstract: In females, pubococcygeus muscle (Pcm) is multifunctional due to its participation in micturition, defecation, dorsiflexion (lordosis) evoked by male stimulation during copulation. Pcm also increases intravaginal pressure, and participates in tail deviation to facilitate penile intromission. Moreover, it has been described that Pcm is reflexively activated by stimulation of perigenital skin, distal vagina, and clitoris from which is known that at least 3 spinal interneurons participate in its activation. In males, Pcm participates in micturition and ejaculation. However, it is unknown which perineal areas participates in Pcm reflex activity (if any) and if this reflex activity is conditioned by gonadal hormones as in females. Thus, we explored Pcm reflex activity by mechanical stimulation of perigenital areas such as scrotum, perineal skin, and glans penis of intact and castrated animals. Results: In males Pcm reflex activity is also present and is characterized by discharges with different amplitudes and frequencies. In intact rats, perineal

skin brushing, pressure to scrotum and/or to glands penis produced tonic *"on"* and *"off"* (after-discharges) responses; while, phasic *"on"* and *"off"* responses were obtained only during pressure of scrotum and/or glans penis. Surprisingly, in castrated rats we found that Pcm reflex activity is highly sensitized i.e. perineal skin brushing, and pressure to scrotum produced tonic *"on"* and *"off"* responses with higher frequencies and longer duration than intact rats. Meanwhile, phasic "on" and "off" responses were present in perineal skin, and pressure to scrotum and/or glans penis. Discussion: In female, estradiol is acting as a neuromodulator on this reflex activity, as long-lasting after-discharges of Pcm motoneurons are noticed in proestrous or estradiol-treated rats. Surprisingly, castration promotes the onset of this reflex activity sensitization in males. Therefore, other gonadal hormones namely testosterone and/or dihydrotestosterone are involved in Pcm reflex activity modulation, which is important for processes such as ejaculation or micturition.

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Poster

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Topic: E.09. Motor Neurons and Muscle

Support: NIH Grant R44NS077526
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De Luca Foundation, MA

Title: Strategy of motor unit activation during eccentric and concentric dynamic contractions

Authors: J. LETIZI, B. SHIWANI, J. C. KLINE, S. ROY, G. DE LUCA, *P. CONTESSA; Delsys & Altec Inc., Natick, MA

Abstract: Distinct neural control strategies have been postulated during the execution of eccentric vs. concentric muscle contractions [1]. However, since traditional methods for investigating motor unit behavior are limited to isometric conditions, the strategies employed by the nervous system to regulate different types of dynamic activities remain unknown. We used a non-invasive system of wearable sensors and automated motor unit extraction algorithms to reveal the neural strategy that regulates concentric vs. eccentric contractions in the Biceps Brachii. N=5 healthy subjects (3 male, 2 female, 23-31 years old) were asked to perform repeated elbow flexion/extension curls while holding a 10 lbs weight. Elbow joint angle was monitored using an electrogoniometer (Biometrics, UK). A surface array sensor placed on the skin over the Biceps Brachii recorded four concurrent electromyographic (sEMG) signals,

filtered between 20-450 Hz and sampled at 2 kHz (NeuroMap™ System, Delsys, MA). The sEMG signals were decomposed into the constituent motor unit action potential (MUAP) shapes and firing instances using novel decomposition algorithms designed to identify and track MUAPs throughout dynamic movements [2]. Consistent with previous findings, the size principle of motor unit recruitment was maintained in both concentric and eccentric contractions [3]. We also make a novel observation that, even though motor units displayed higher firing rates during the concentric phase, the firing rate vs. MUAP amplitude relation showed consistent adaptations during both phases, indicating that the firing rate organization of the motor unit pool is invariant to the task. This finding supports the existence of a unique neural strategy that regulates motor unit behavior during concentric vs. eccentric tasks in which motor unit firing modulation is driven by the varying mechanical demands of the tasks.

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References

[1] Enoka et al. J Appl Physiol 1996.
[2] De Luca et al. J Neurophysiol 2015.
[3] Chalmers. Sports Biomechanics 2008.

Disclosures: **J. Letizi:** A. Employment/Salary (full or part-time):; Delsys & Altec Inc. **B. Shiwani:** A. Employment/Salary (full or part-time):; Delsys & Altec Inc. **J.C. Kline:** A. Employment/Salary (full or part-time):; Delsys & Altec Inc. **S. Roy:** A. Employment/Salary (full or part-time):; Delsys & Altec Inc. **G. De Luca:** A. Employment/Salary (full or part-time):; Delsys & Altec Inc. **P. Contessa:** A. Employment/Salary (full or part-time):; Delsys & Altec Inc..

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.15/P29

Topic: E.09. Motor Neurons and Muscle

Title: Differential adjustments to low and high threshold motor units during experimental muscle pain

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Abstract: Most of the knowledge about motor unit control strategies during painful conditions comes from research performed during low-force sustained contractions. These previous studies have recognized that discharge rate decreases when nociceptive substances are infused into the muscle [1]. Despite this consistent observation, it is not currently known how the central nervous system controls motor unit behavior during painful muscle conditions at higher levels of excitation [i.e. forces closer to the maximum voluntary contraction (MVC)]. In this study, we aimed to compare the behavior of tibialis anterior motor unit firing properties during low (20% MC) and high-force (70% MVC) contractions in four conditions: baseline (no pain), isotonic (injection of control non-painful solution to the muscle), pain (injection of hypertonic saline solution) and post-pain. Surface EMG signals were recorded from 15 participants (26 (3) years, 6 females) using a matrix of 64 electrodes while performing ankle-isometric dorsiflexion. Signals from the four different conditions were decomposed and the same motor units were tracked across conditions [2, 3]. The amount of neural drive received by the motor unit pool at each force level was estimated by calculating the difference in discharge rate from recruitment to target torque [4]. At 20% MVC, motor unit discharge rate and estimated neural drive decreased significantly during pain (baseline vs. pain: 12.7 (1.1) Hz to 11.5 (0.9) Hz, $p<0.001$), without observing any other adjustment to motor unit properties. In contrast, at 70% MVC, discharge rate and estimated neural drive increased significantly during the painful condition (baseline vs. pain: 19.7 (2.8) Hz to 21.3 (3.5) Hz, $p=0.029$). These changes were also accompanied by a decrease in recruitment threshold (baseline vs. pain: 59.0 (3.9) %MVC to 55.9 (3.2) %MVC, $p=0.02$). Results from this study show that there is a differential adjustment among low and high-threshold motor units during painful conditions. Increases in synaptic input to high threshold motor units might be likely required to engage fast muscle fibers in order to move away from the painful stimuli, and thus prevent further damage to muscle tissue.
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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

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Topic: E.09. Motor Neurons and Muscle

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Title: Factors influencing estimation of motoneuron excitability using analysis of motor unit populations

Authors: *L. M. MCPHERSON[1,2], A. S. HASSAN[3], F. NEGRO[6], M. CUMMINGS[4], R. K. POWERS[7], J. P. DEWALD[4], C. HECKMAN[5], C. K. THOMPSON[8];
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Abstract: Neuromodulatory synaptic inputs to motoneurons (via 5-HT and NE) have a dramatic influence on motoneuron excitability, in part because they facilitate induction of persistent inward currents (PICs). PICs lead to amplified and prolonged motoneuron output in response to excitatory synaptic inputs, which appropriately scales motoneuron output according to task demands. This ability is an essential component of neural control of movement, and its disruption has been implicated in motor deficits in populations with neurological injury.
The standard method for estimation of neuromodulatory synaptic input and PIC amplitude is to quantify recruitment/de-recruitment hysteresis during slow linear “triangle” contractions through a paired motor unit analysis (F).
The F technique requires that motor units pairs must meet certain criteria based on assumptions related to the underlying physiology, e.g., motor unit pairs must have sufficient correlation of their firing rates, as the firing rate trajectory of the lower threshold (control) unit is used as an approximation of the ionotropic excitatory synaptic input to the higher threshold (test) unit. The difference in recruitment time between the control and test units must be long enough to ensure the PIC of the control unit is fully active before test unit recruitment. Firing rate saturation in the control unit may also bias the F calculation and is often controlled for. Despite these standard criteria, the specific threshold values for each criterion vary across studies, as do computational factors such the type of firing rate smoothing filter and the accuracy of motor unit spike times. The purpose of this study is to determine the sensitivity of F to differences in the factors discussed above. To estimate motoneuron firing rates in humans, we used a high-density surface EMG decomposition to obtain motor unit spike times, in combination with a custom semi-automatic editing tool to improve accuracy. This approach provides spike times from large populations of motor units, which enables a robust, systematic analysis of factors influencing the estimation of PICs in humans. Here we present findings of this systematic analysis applied to data from the triceps of 10 healthy participants during isometric triangle contractions.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.17/P31

Topic: E.09. Motor Neurons and Muscle

Title: The need of accurate decomposition methods for the precise estimation of the neural drive to muscle

Authors: *F. NEGRO[1], E. MARTINEZ-VALDES[2], L. M. MCPHERSON[3], C. K. THOMPSON[4], A. CUDICIO[1], U. YAVUZ[5];
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Abstract: Decomposition of the electromyographic (EMG) signals can provide essential information about central and peripheral properties of motor units (MUs). Recently, high-density (HD) multi-channel electrode systems have been developed for surface EMG detection. HD-EMG overcomes the classical bipolar detection and provides detailed spatial information of the electrical activity over a large portion of the muscle. When tens of EMG channels are available, convolutive blind source separation can be used for the automatic decomposition. The “blind” separation of concurrently active MUs is based on the statistical properties of sources, not on expected discharge patterns of motor unit. Becaue of this, the extracted solutions do not always correspond to physiological MU firing patterns. For this reason, measures of reliability have been developed (e.g. Silhouette (SIL) [1]) as a surrogate measure of decomposition accuracy and automated exclusion of non-physiological MUs. However, even using high values (e.g. SIL=0.85-0.90), a number of firings may be still erroneous. In these cases, visual inspection from an expert operator may be used to supplement the capability of the automatic algorithm to resolve erroneous firings. In this study, we aimed to compare the decompositions extracted from the fully automatic method [1] with the ones subsequently edited by an expert operator (semi-automatic). The semi-automatic method provides the possibility to update the automatic decomposition results by iterative visual editing of the individual discharge times and the verification of the improvement in the estimation of the sources. Results are reported for four subjects in the Vastus Lateralis muscle over a wide range of contraction intensities. Average discharge rates of the extracted MUs were similar between the automatic and semi-automatic methods (11±2 vs 11±2 pps). On the other hand, Coefficient of Variation (19±3 vs 15±2%) and Force Recruitment Threshold (35±2 vs 32±3%) were significantly lower in the semi-automatic method ($P<0.05$). Similarly, the correlation between neural drive and force well as the coherence between spike trains were significantly higher in the semi-automatic case. These data

demonstrate some motor unit parameters are particularly sensitive to the erroneous identification of discharges by automatic decomposition methods and, therefore, the results of these methods should always be processed by accurate techniques and verified by visual inspection. [1] Negro et al. (2016) J Neural Engineering. * All authors contributed equally to this study

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

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Program #/Poster #: 495.18/P32

Topic: E.09. Motor Neurons and Muscle

Support: NS098509

Title: Within and across day repeatability of estimates of human spinal motoneuron excitability

Authors: *C. K. THOMPSON[1], T. KMIEC[1], P. KUMAR[2], L. M. MCPHERSON[3], F. NEGRO[4];
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Abstract: The discharge of a spinal motoneurons and the contraction of its associated muscle fibers represents the smallest quanta of motor output. The discharge of a spinal motoneuron is regulated not only by its synaptic input, but also by its intrinsic excitability. Though we are not yet able to directly measure the excitability of human spinal motoneurons, approaches have been developed to estimate the synaptic input to human spinal motoneurons by substituting the current injected by an invasive microelectrode with the discharge of a low threshold motor unit during time varying volitional contractions. Using pairs of motor unit discharge receiving similar synaptic input, the excitability of a spinal motoneuron can be assessed by quantifying the difference in frequency of a low threshold unit at the recruitment and derecruitment of this higher threshold motor unit (delta-f). Understanding the excitability of human spinal motoneurons is of interest in a number of aspects of motor control, however the repeatability of this measure is unknown. Here twelve individuals completed three sets of three dorsiflexion contractions over three nonconsecutive days. Surface electromyographic signals are collected from the tibialis anterior using a 64-channel electrode matrix. Offline, signals were decomposed into their corresponding motor unit action potential spike trains using a well-validated convolutive blind source separation approach; each unit was visually inspected for accuracy. Within each of these 324 contractions, an average of 21±8 motor units were decomposed resulting in 171±135 delta-f comparisons per contraction. No differences in delta-f estimates

were observed across contractions, sets, or days. Intraclass correlation coefficient analyses (2,1) demonstrates the average delta-f measure has poor test-retest reliability across three consecutive contractions, whereas moderate reliability is observed across sets and days. When motor units are tracked across contraction and only the same motor unit pairs are assessed across trials, repeatability values were even lower than when using the population data. These data demonstrate the delta-f measure is variable across repeated contractions, though this variability decreases with increased number of observations. Further, these data point to the utility of population data for this approach. It remains unclear if this variability is due to error of measurement or if this variability reflects the underlying physiological processes.

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Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

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Topic: E.05. Brain-Machine Interface

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Title: Striatopallidal pathway modulates neuroprosthetic learning by volitional control of calcium signals in the cortex & globus pallidus

Authors: *J.-F. CHEN[1], L. ZHANG[1], Y. ZHOU[1], C. LIU[1], W. ZHENG[1], Z. YAO[1], Q. WANG[1], Y. JIN[2], S. ZHANG[2], W. CHEN[2];
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Abstract: Brain-machine interfaces (BMI) hold promise for restoring motor function for disabled patients and providing a novel approach to sensorimotor learning. At the core of BMI adaptation is neuroprosthetic learning by volitional control *(independent of movement)*, but their neural circuit and neuromodulator bases are largely unexplored. To better define the volitional control mechanisms at the cellular level, we have developed a calcium-based neuroprosthetic task in which mice were conditioned to volitionally increase calcium signals above the specified threshold for the reward independent of movement. Using calcium activity as a volitional controller, we revealed, with the neural activity-behavior causality, the distinct neuroplasticity changes during neuroprosthetic learning and in response to the decoder changes. Importantly, we have demonstrated, for the first time, that the calcium signal in the globus pallidal neurons (the striatopallidal output nucleus) acted as a volitional controller signal to support the development

of neuroprosthetic learning. Furthermore, we demonstrated that pharmacological blockade adenosine A_{2A} receptors (highly enriched in the striatopallidal pathway) facilitated neuroprosthetic learning and converted an ineffective conditioning protocol to the effective for neuroprosthetic learning. Collectively, these findings define striatopallidal pathway control of neuroprosthetic learning and suggest a novel neurorehabilitation strategy to improve neuroprosthetic learning by pharmacological targeting the striatopallidal A_{2A} receptor.

Disclosures: **J. Chen:** None. **L. Zhang:** None. **Y. Zhou:** None. **C. Liu:** None. **W. Zheng:** None. **Z. Yao:** None. **Q. Wang:** None. **Y. Jin:** None. **S. Zhang:** None. **W. Chen:** None.

Poster

495. Brain-Computer Interface: Neurophysiology, Function, and Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 495.20/P34

Topic: E.05. Brain-Machine Interface

Support: DFG-FOR1847
DFG-SFB889

Title: Adaptation of neural activity in parietal cortex of rhesus monkey during control of 3D reaches in a brain-computer interface

Authors: ***E. FERREA**[1], P. MOREL[1], A. GAIL[1,2,3];
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Abstract: Posterior parietal cortex (PPC) is known to integrate visual and proprioceptive sensory information, e.g. about the position of the own hand during reaching. In a joystick task with curved trajectories, activity in PPC was previously shown to correlate better with the immediate (zero time-lag) cursor direction than with its previous positions (Mulliken et al. 2008), arguing against mere sensory encoding. Such findings support the idea that PPC contributes to internal forward model computations and real-time state estimation for online motor control: it could combine expected with actual sensory feedback to form an inner belief of how motor commands affect the state of the body. From previous studies it is unclear if neural encoding is more compatible with the idea of an efference copy, the predicted sensory feedback (visual or proprioceptive) or a state estimation, since in manual task these parameters are typically confounded. We here used a brain-computer interface (BCI) to study motor control with the cursor motion (the motor command) being fully experimentally controlled and proprioceptive feedback being held constant. In different sessions, a BCI decoder was linked to different populations of neurons, i.e., subsets of primary motor (M1) and dorsal premotor cortex (PMd)

units. The complementary subset of M1 and PMd neurons, and all PPC units, were not linked to motor output controlled by the decoder. We applied a visuomotor rotation paradigm to dissociate visual feedback from motor representation.
Results show that over the course of adaptation to the perturbation, neurons in all three brain areas coherently shifted their tuning to counteract the applied visuo-motor rotation, irrespective of being part of the BCI decoding units or not. PPC units thereby better predicted the direction from the immediate cursor position towards the static goal rather than the actual cursor movement direction, inconsistent with the idea of an efference copy signal. To test if visual or motor-related encoding determined this PPC activity, we trained an offline decoder based on PPC activity during unperturbed baseline trials and applied it to perturbed rotation trials. PPC population activity consistently encoded adaptive changes that did not reflect changes in the visual input but matched the changing motor output. Trial-to-trial updating of the decoded cursor trajectories from PPC correlated with the acquired behavioral improvements. In conclusion, our findings support the hypothesis that PPC reflects a real-time state estimation of immediate cursor-to-target direction in a motor reference frame suited for online control and error correction of movements.

Disclosures: **E. Ferrea:** None. **P. Morel:** None. **A. Gail:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.01/P35

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Effects of inter-stimulus interval duration and predictability on sensorimotor beta

Authors: *R. B. LERICHE, N. JACKSON, K. PETERSON, Z. ASPANDIAR, V. HUFNAGEL, N. C. SWANN;
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Abstract: Introduction: In motor tasks, the inter-stimulus interval (ISI) between the fixation-cue and go-cue can have a varied, jittered, or fixed duration. This period is often used as a baseline period for electroencephalography (EEG) studies as a comparison for subsequent motor-related activity. Choosing how the ISI is set may unpredictably impact subsequent motor responses as both motor preparation and execution involve modulation in the beta frequency range (13-30 Hz). Moreover, purely visual processing is also associated with beta modulation in several areas including the sensorimotor cortex. Our observations affirm how beta activity during preparatory intervals may influence neural processing during motor responses.
Methods: We conducted a delayed-go task with blocks of fixed or varied ISIs (block-order randomized). The task began with a fixation cue, followed by an arrow (go cue) pointing left or

right. Participants responded via button presses using their right hand. The ISI for fixed blocks was 500ms and for varied blocks, the ISI was randomly selected per trial to be 300, 400, 500, 600, or 700ms. Healthy participants aged 18-30 (n=14) completed both blocks with concurrent scalp EEG. We focused our analysis on data from the electrode over left sensorimotor cortex (C3), contralateral to the responding hand. We calculated beta power using the pwelch function in MATLAB for the ISI epoch of each trial and then averaged across trials.
Results: Between all fixed and varied ISI conditions the average beta power from electrode C3 was significantly lower in the fixed versus varied ISI condition (Wilcoxon's signed rank test, p= 0.0064). The average beta power from electrode C3 was significantly lower in the fixed blocks versus varied trials of 500ms duration (Wilcoxon's signed rank test, p= 0.0070). There were no differences across the varied ISI duration (i.e. comparing 300, 400, 500, 600, and 700ms ISI varied trials, Kruskal-Wallis test, p= 0.979).
Discussion: These results suggest that predictability of the timing of forthcoming motor responses is associated with reduced beta. Since beta power decreases are associated with motor preparation and execution we suspect that this reduced beta power may be a manifestation of motor preparation with known go cue timing. These preliminary results suggest a need to further examine the relationship between peri-movement beta modulations and the need for careful consideration of the ISI in task design.

Disclosures: R.B. Leriche: None. **N. Jackson:** None. **K. Peterson:** None. **Z. Aspandiar:** None. **V. Hufnagel:** None. **N.C. Swann:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.02/P36

Topic: E.07. Rhythmic Motor Pattern Generation

Support: JUMP-ARCHES

Title: A neuromechanical model of continuous wrist motion

Authors: *L. ZIEGELMAN[1], R. SUN[1,2], Y. HU[1], W. A. DELGADO[1], M. E. HERNANDEZ[1]; [1]Univ. of Illinois At Urbana-Champaign, Urbana, IL; [2]Sch. of Med., Case Western Reserve Univ., Cleveland, OH

Abstract: This study aimed to create a neuromechanical simulation of wrist motion in six degrees of freedom. This is done by adapting a previously proposed neuromechanical model of hand pronation and supination to also model hand flexion, extension, radial deviation, and ulnar deviation. This model explores the effectiveness of adapting a Matsuoka Oscillator to account for continuous wrist motion and is personalized to account for physiological changes to the

neuromechanical system due to aging. Both healthy young and older adults (HYA, HOA) performed three trials of continuous wrist motion in all six degrees of freedom for 20 seconds while wearing a research grade IMU (InertiaCube BT) to validate the kinematics of the theoretical model. The proposed model is shown to be flexible to modeling multiple modalities of wrist motion and is validated using experimental data.

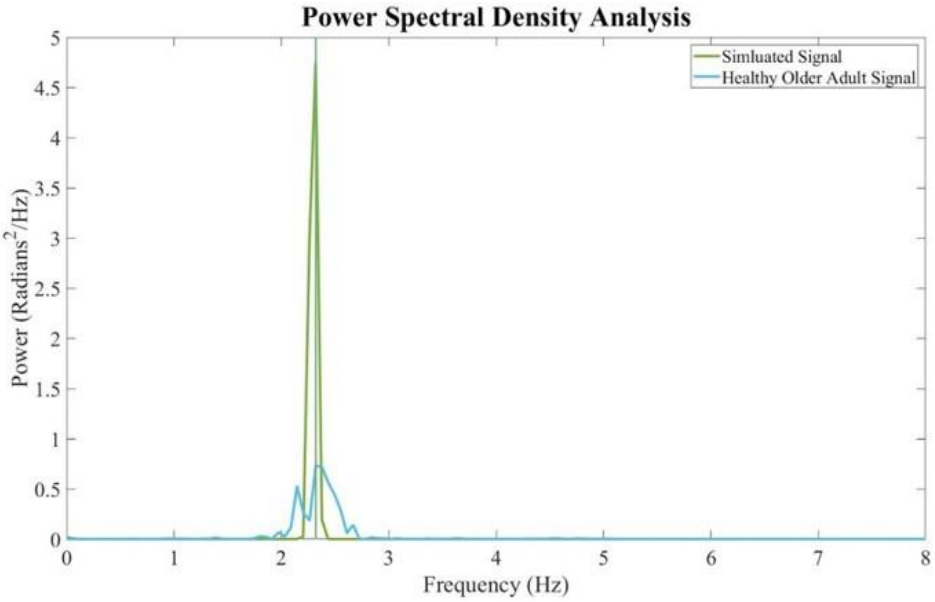

Fig 1. A power spectral density analysis of the flexion and extension simulation in healthy older adults showing model fit.

Disclosures: L. Ziegelman: None. **R. Sun:** None. **Y. Hu:** None. **W.A. Delgado:** None. **M.E. Hernandez:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.03/P37

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH R01-HD087089

Title: Transient behavior and predictability in manipulating complex objects

Authors: *R. T. NAYEEM[1], S. BAZZI[1], N. HOGAN[2], D. STERNAD[3];
[1]Northeastern Univ., Boston, MA; [2]MIT, Cambridge, MA; [3]Departments of Biology, Electrical & Computer Engineering, and Physics, Northeastern Univ. Dept. of Biol., Boston, MA

Abstract: Humans dexterously manipulate a wide variety of complex objects. A mundane example is transporting a cup of coffee: the hand applies a force to the cup, and also indirectly to the liquid, which in turn acts back on the hand. Previous work in our lab investigated how humans tune into resonant frequencies when rhythmically moving a dynamic object. Unlike in free movements, subjects did not minimize effort but adopted strategies that rendered interactions predictable. In those studies subjects started from rest, always at the same initial conditions; the transient was excluded from analysis, focusing on steady state behavior. As transients can be complex, depending on initial conditions, this study examined whether humans choose initial conditions to reduce transient duration prior to reaching steady state. We hypothesized that subjects find initial conditions that minimize the transient duration and settle to steady state behavior that renders object dynamics predictable.
The experimental task consisted of interacting with an object simulated by a robot with haptic feedback. The cup of coffee was simplified to a cart-and-pendulum system moving on a horizontal line; the subject moved the cart, while the pendulum only moved indirectly. The cart-pendulum system was visually presented as a ball rolling in a cup. Importantly, movements of the cup also accelerated the ball, which in turn acted back on the hand. Participants moved the cup back and forth rhythmically between two targets paced by a metronome at 0.6Hz without losing the ball. They were instructed to explore their initial conditions within a start box before initiating the rhythmic movement by exiting the start box when they were ready. Participants performed 120 trials, each 15s excluding pre-trial exploration. Dynamic simulations were performed to understand the effect of initial conditions. To calculate transient duration, steady state started at the time when relative phase between ball and cup was close to zero. Mutual information between applied force and cup motion evaluated predictability of the steady state behavior.
Preliminary results showed that subjects converged to a small set of initial conditions, they decreased the transient duration with practice and established a steady state defined by relative phase between cup and ball; mutual information increased with practice. Simulations confirmed that these initial conditions corresponded to shorter transients. These results present first support for our hypothesis that humans can identify initial conditions that minimize transients and favor steady state behavior that enhances predictability.

Disclosures: **R.T. Nayeem:** None. **D. Sternad:** None. **S. Bazzi:** None. **N. Hogan:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.04/P38

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Foraging as an evidence accumulation process

Authors: *J. DAVIDSON[1], A. EL HADY[2];
[1]Collective Behavior, Max Planck Inst. for Ornithology, Konstanz, Germany; [2]Princeton Neurosci. Inst., Princeton, NJ

Abstract: The patch-leaving problem is a canonical foraging task, in which a forager must decide to leave a current resource in search for another. As a decision task, patch-foraging is a behavior that can be directly linked to fitness; theory and experiments have derived optimal strategies and tested for conditions where animals do or do not follow them. Although a mechanistic decision model is needed to interpret experimental studies regarding the neural mechanisms behind foraging decisions, current models of patch-leaving decisions do not consider the imperfect and noisy sampling process through which an animal gathers information. In this work we formulate a mechanistic model of patch-leaving decisions by linking ecological models of the patch-leaving task with models of evidence accumulation that are used in systems neuroscience. We solve the model for conditions where foraging decisions are optimal and equivalent to the marginal value theorem, and perform simulations to analyze deviations from optimal when these conditions are not met. By adjusting the drift rate and decision threshold, the model can represent different strategies, for example an incremental, decremental, or counting strategy. These strategies yield identical decisions in the limiting case but differ in how patch residence times adapt when the foraging environment is uncertain. To describe sub-optimal decisions, we introduce an energy-dependent marginal utility function that predicts longer than optimal patch residence times when food is plentiful. Our model opens up a space to study naturalistic decision making in a quantitative manner. We discuss the model in the context of readily existing data sets, as well as how it can be used to plan future experiments which seek to identify neural circuits underlying patch-leaving decisions.

Disclosures: J. Davidson: None. **A. El Hady:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.05/P39

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSF grant IIS-1524647

Title: A computational model of mixed pattern generation for forward locomotion in *C. elegans*

Authors: *E. J. IZQUIERDO[1], E. O. OLIVARES[2];
[1]Cognitive Sci. Program, Indiana Univ., Bloomington, IN; [2]Cognitive Sci. Program, Indiana Univ., Bloomington, IN

Abstract: *C. elegans* locomotes in an undulatory fashion, generating thrust by propagating dorsoventral rhythmic bends along its body. As in many other organisms, there are likely multiple mechanisms, internal and external, contributing to the generation, propagation, and coordination of these rhythmic patterns. Experimental and theoretical work has provided support for the role of both stretch-receptor feedback (SRF) and central pattern generators (CPGs). However, current work leaves a number of major questions unanswered: (1) Can multiple CPGs coordinate their activity to produce the traveling wave necessary for locomotion, in the absence of SRF? (2) Can SRF alone drive locomotion, in the absence of CPGs? and (3) How can SRF and CPGs work together to increase the robustness of the locomotory behavior? In current work, we integrate a neuromuscular model of the ventral nerve cord with a biomechanical model of the worm's body. We then use an evolutionary algorithm to determine unknown physiological parameters of the model so that the complete system reproduce the kinematics of forward locomotion. We performed experiments under three conditions: SRF was never available during evolution; SRF was always available; and SRF was intermittently available. We then analyzed the ensemble of solutions as a way to explore theoretical possibilities to the motivating questions. Under all conditions, the model worms reproduced the speed of the worm and were consistent with key kinematic features of locomotion, including frequency, wavelength and amplitude of bending. From the first condition, we determined that a chain of CPGs, without SRF, can drive forward locomotion on agar. We demonstrate this is feasible through pacemaker neurons as well as intrinsic network oscillations. Analysis of the solutions reveal that motoneuron gap-junctions alone can coordinate anterior-posterior oscillations. In the second condition, when SRF was available, the neural controller takes advantage of this information to both generate and propagate the rhythmic pattern without the need for CPGs. Although other computational models of reflex pattern generation have been published to date, this is the first to account for the size and directionality of the anatomical processes postulated to sense stretch in the worm. Finally, in the third condition, model worms utilize mixed pattern generators: a combination of multiple CPGs that use SRF to fine-tune, coordinate and modulate the motor patterns. We analyze representative solutions from this group in detail to reveal principles underlying the coordination of internal and external mechanisms that generate robust and flexible locomotion in the worm.

Disclosures: E.J. Izquierdo: None. **E.O. Olivares:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.06/P40

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Chewing drives stepping rates regardless of chewing initiation timing suggesting top-down control of coupled oscillators

Authors: *B. SAMULSKI, J. PREBOR, S. MORRISON;
Kinesiology and Rehabil., Old Dominion Univ., Norfolk, VA

Abstract: Chewing plays a vital role in daily life by facilitating nourishment. Walking functions as a primary way to explore and interact with the environment. These two seemingly unrelated tasks appear to share a coupling mechanism when performed together. The directionality of this relationship has not been well studied, so little is known about the nature of how these coupled oscillators coordinate. Previous research has initiated chewing prior to performing the secondary task and consistently sets the rate of performance of the coordinated action. Previous research suggests a top-down control model, whereby chewing entrains stepping. An alternative theory that the movement performed first, temporally, could set the coupling pattern between actions remains plausible. The aim of this study was to investigate whether initiating chewing before or during gait affects walking patterns. Fifteen healthy young (18-40) and fifteen older adults (age 60-75) participated in the study. Individuals were asked to chew at three different speeds: 1. preferred, 2. self-selected slow, and 3. self-selected fast. Chewing rates were recorded using surface EMG recordings from the masseter muscles. This was performed while the person stood (baseline) and when walking over a pressure sensitive walkway. For the gait tasks, chewing was introduced either prior to the beginning of the walk or mid-way through the walking trial. Participants self-selected the walking speed for all trials. A baseline assessment of each person's gait was performed with no concurrent chewing. Gait parameters such as step/ stride length, gait velocity, step cadence, and step time were measured. Fast chewing and slow chewing were associated with changes in step cadence. Overall, the results indicate that the timing of when chewing began did not alter how stepping rates were influenced. When chewing was performed prior to walking, the step rate coupled in a 1:1 manner to the chewing rate across all chewing speed conditions. When chewing began during gait, the step rate coupled to the chewing rate in a 1:1 ratio for each of the trials. Coupling of the two continuous motor tasks may indicate that neural mechanisms which dictate timing of tasks, such as central pattern generators for the mouth and limbs, may be interconnected. The relationship describing the interplay between neural oscillators during performance of simultaneous tasks is not clear. The bilateral innervation of chewing musculature, as well as the proximity of chewing control centers in the midbrain, support a hierarchical influence of chewing rates on gait.

Disclosures: B. Samulski: None. **J. Prebor:** None. **S. Morrison:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.07/P41

Topic: I.06. Computation/ Modeling/ and Simulation

Title: A hybrid modeling framework for the comparison of motor and sensory peripheral nerve fiber recruitment during stimulation

Authors: *S. ROMENI[1], G. VALLE[1,2], A. MAZZONI[1], S. MICERA[1,2];
[1]Translational Neuroengineering Lab., The Biorobotics Institute, Scuola Superiore Sant'Anna, Pontedera, Italy; [2]Ctr. for Neuroprosthetics and Inst. of Bioengineering, École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland

Abstract: The importance of modeling in the field of neuroprosthetics is hardly overestimated: invasive implants are expensive and require the joint efforts and interplay of teams of experts from several different backgrounds. Modelling could concurrently enhance both the effectiveness and the efficiency of neuroprostheses accompanying the whole process from experimental planning to the interpretation of the obtained results. Moreover, the comparison of alternative models for a given phenomenon could contribute and shed some light on the underlying processes providing an invaluable tool for progressive scientific research.
We employed the framework of hybrid modeling, a computational model based on the separation of the two problems of (1) volume conduction in naturalistic structures of the charge injected by an electrode and (2) determining the consequent response of the targeted nerve fibers.
Different levels of approximation were defined for the geometries of mammal spinal nerves, and the geometries of an intraneural (TIME) and an extraneural (FINE) electrodes were defined parametrically. Such nerves were populated with naturalistic fiber samples both in terms of diameter distributions which were efficiently packed in the physiological structures. The problem of the determination of the most adequate family for the fiber diameter distribution was studied, leading to the choice of adequate beta mixture distributions.
The recruitment properties of motor and sensory nerve fibers in terms of recruitment curves and global and local selectivities were compared through the implementation of computational models found in literature, which were previously extensively characterized for the current use through the simulation of their stimulation with a point electrode in a homogeneous medium.
Then two realistic stimulation settings (corresponding to intraneural and extraneural stimulation experiments) were studied, in which it appeared clearly how the different physiology of motor and sensory fibers - embodied in the employed models as different Hodgkin-Huxley parameters for the ion channel equation corresponding to Ranvier nodes - had drastic consequences on the recruitment of the two modeled fiber types.
The present work could be generalized through reciprocity arguments to neural signal recording simulation as well, thus providing a tool for the complete characterization of bidirectional prostheses. The intrinsic conceptual modularity of the modeling flow could moreover allow the inclusion of more fiber types for the simulation of a great variety of applications and implants.

Disclosures: **S. Romeni:** None. **G. Valle:** None. **A. Mazzoni:** None. **S. Micera:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.08/P42

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant 1DP2NS111817-01
NIH Grant 5T32MH020068-15

Title: Decoding motor tasks through supervised subspace alignment

Authors: *I. PENIDO[1,2], J. B. HYNES[3], J. P. DONOGHUE[4], C. E. VARGAS-IRWIN[1];
[1]Neurosci., Brown Univ., Providence, RI; [2]Carney Inst. for Brain Sci., Providence, RI;
[3]Neurosci., Brown, Providence, RI; [4]Wyss Ctr. For Bio and Neuro Engin., Geneva, Switzerland

Abstract: Within a species, the brains of different individuals are laid out according to general stereotyped patterns. However, the precise microstructure of each resulting brain network is unique. For vertebrates, there is not a one-to-one correspondence between the neurons in one subject and those in another, so it is not possible to directly map activity patterns across different brains. However, when individuals from the same species perform a given behavioral task, it is reasonable to assume that their brains are performing equivalent computations: although the precise activity patterns may differ, the relationship between the sets of patterns observed in each brain is likely to be similar. Neural computation occurs in subject-specific high dimensional substrates. However, the activity patterns recorded for a given behavioral task tend to be concentrated in relatively low dimensional sub spaces (commonly referred to as neural 'manifolds', although they do not necessarily conform to the formal mathematical definition). We propose that brains performing equivalent computations will operate on manifolds with similar topological structure. Building on this basic idea, we present a computationally accessible method that uses similarity-based clustering (Vargas-Irwin, 2015), followed by an optimized linear transform to align neural data from different brains into a common unified state space (USS) representation.
We examined the potential for universal decoding models applicable across different subjects and sessions using M1 cortical data from three macaque monkeys performing two different tasks: a center-out radial reaching task (including 8 different reach directions), and a grasping task (including 3 different grips).
Our results show that small samples of data (approximately 5 exemplars for each movement category) are sufficient to find the projection matrix into an existing USS. In this way, the amount of data available to train classifiers can be greatly increased, significantly improving discrete movement classification accuracy (for either reach direction or grip type). Our results support the idea that the structure of task-related manifolds tends to be preserved across subjects

and sessions, and suggest that decoding models applicable across different brains at the level of single units are viable.

Disclosures: I. Penido: None. **J.B. Hynes:** None. **J.P. Donoghue:** None. **C.E. Vargas-Irwin:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.09/Q1

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Horizon2020 grant 720270
Horizon2020 grant 785907
The Swedish Research Council
Swedish e-Science Research Center
Swedish National Infrastructure for Computing (SNIC) at PDC KTH

Title: Large scale *in-silico* striatum reconstruction on the micro-circuitry level

Authors: *J. HJORTH[1], A. KOZLOV[1], J. FROST NYLÉN[2], I. CARANNANTE[1], R. C. LINDROOS[2], S. MYSORE SURYANARAYANA[2], G. SILBERBERG[2], J. HELLGREN KOTALESKI[1], S. GRILLNER[2];
[1]Dept. of Computer Sci. and Technology, Sch. of Electrical Engin. and Computer Sci., Royal Inst. of Technol., Stockholm, Sweden; [2]Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden

Abstract: The basal ganglia are an evolutionary conserved subcortical nuclei involved in action selection and learning. Their importance is highlighted by the severity of the diseases affecting it, such as Parkinson's and Huntington's, and a variety of psychiatric diseases. The striatum, the largest structure of the basal ganglia, is the main input stage. For the striatal projection neurons (direct and indirect type), fast spiking interneurons, cholinergic interneurons and low threshold spiking interneurons there exist detailed information about electrophysiology, but only sparse data of the neuronal connectivity.
We present a large scale in-silico reconstruction of the mouse striatum micro-circuitry, based on somato-dendritic-axonal morphologies and detailed compartmental models of each neuron subtype optimised using BluePyOpt to match experimental elecrophysiological recordings. The striatal neurons are randomly placed within a 3D volume corresponding to the striatal structure (mesh downloaded from Allen Institute for Brain Science), with densities of the different types of neurons matching that seen in experiments. Putative synapses are detected using a touch detection algorithm, which is he pruned by a set of rules based on connectivity data, giving the

final set of synapses.
The striatal microcircuit model is simulated using Parallel Neuron on a Cray XC40 machine. The striatal network is driven by simulated cortical and thalamic input. Using this network model we can investigate the role of the principal neutrons as well as their interactions with the subgroups of interneurons in the circuit.
This study is funded by: Horizon2020 grant agreement 720270 and 785907 (Human Brain Project, SGA1 and SGA2); The Swedish Research Council; Swedish e-Science Research Center. The network model is simulated on a Cray supercomputer provided by the Swedish National Infrastructure for Computing (SNIC) at PDC KTH.

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Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.10/Q2

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant NS097781

Title: A modeling and optimization framework for understanding the role of reflexes in the feline hindlimb in promoting proportional coordination of the joints during yield

Authors: *T. GOVINDARAJ[1], D. R. HOWLAND[4], G. SAWICKI[2], T. R. NICHOLS[3];
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Abstract: Proprioceptive pathways arise from a variety of receptors, including muscle spindles and Golgi tendon organs. Muscle spindles measure changes in length and velocity, while tendon organs measure active contractile force. Force feedback is more widely distributed than length-dependent feedback pathways, so force-dependent pathways are likely to regulate inter-segmental coordination. During the yield, or weight acceptance phase of locomotion, the knee and ankle obey proportional coordination [1], or equal joint angle excursions. To understand how force feedback can help promote proportional coordination, we are developing a three segment model of a feline hindlimb in Simulink, with realistic lengths and masses and a rotational spring and damper at each joint to represent the intrinsic properties of muscle with integral stretch reflexes. Based on the known distribution of muscular mass, joint impedance decreases from hip to ankle. In this initial version of the model, there is no provision for biarticular muscles. Force

feedback is represented by a matrix multiplying the joint torques. To simulate the limb's behavior during yield, the initial configuration is set as the beginning of the weight acceptance phase (E2), and a force equivalent to the maximum ground reaction force experienced during yield in level walking is applied over 50 ms. We are using a proportionality index to investigate whether this coordination is accomplished by intrinsic neuromechanical properties alone or whether intermuscular reflexes are necessary. As expected from the non-uniform distribution of impedance, the magnitude of joint flexion due to the perturbation decreases from ankle to hip with no interjoint force feedback, and the measure of proportional coordination is 1.05*10^6. We are currently evaluating the effects of interjoint feedback according to patterns observed experimentally. These patterns include gradients of feedback from proximal to distal, distal to proximal, or focused on the ankle musculature. Initial trials with uniform magnitudes of interjoint force feedback resulted in a proportionality index of 1.28*10^6, which is 21.4% greater than the index of the intrinsic neuromechanical properties alone. Therefore, this result supports our hypothesis that proportional coordination is accomplished by interjoint force feedback. Future versions of the model will include coupling terms to represent biarticular muscles, and the use of an optimization approach to determine what patterns of feedback would result in proportional coordination. Funded by NS097781 (DH and TRN), Rebecca F. Hammond Chair (DH) [1] Goslow GE et al. (1973). *J. Morph.*, **141**:1-42.

Disclosures: T. Govindaraj: None. **D.R. Howland:** None. **G. Sawicki:** None. **T.R. Nichols:** None.

Poster

496. Motor Systems Analysis and Models

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 496.11/Q3

Topic: E.07. Rhythmic Motor Pattern Generation

Title: Resting state auditory motor functional connectivity and dopaminergic responses during rhythmic auditory motor entrainment: A [11C]-(+)-PHNO PETand fMRI study

Authors: *Y. KOSHIMORI[1,2], A. P. STRAFELLA[2], M. VALLI[2], V. SHARMA[1], P. RUSJAN[2], S. HOULE[2], M. H. THAUT[1,2];
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Abstract: Auditory-motor entrainment using rhythmic auditory stimulation (RAS) has been shown to improve motor control in healthy persons and persons with neurological motor disorders such as Parkinson's disease and stroke. Neuroimaging studies have shown the modulated activity in the areas of corticostriatal and corticocerebellar circuits in response to RAS. Our previous study showed that the presence of RAS significantly improved the finger

tapping performance measured using absolute tapping period error and its variability and resulted in less dopamine (DA) response in the left ventral striatum (VS) in eight young healthy adults (Koshimori et al., 2019). However, we did not find any correlations between the behavioral and neuroimaging data. This may be because the motor improvement is more associated with brain function on a circuit level. As resting-state functional connectivity (rs-FC) predicts task performance, we sought to investigate the relationships between rs-FC, and DA and behavioral changes between task conditions (i.e., finger tapping performance with and without RAS) in these participants. The resting-state functional MRI data were preprocessed and analyzed using CONN functional toolbox. The seed ROIs included bilateral auditory areas. We found several auditory motor pathways that showed significant correlations with changes in the behavioral measures. Among them, rs-FC between left Planum Polare and left SMA also showed a significant correlation with the DA changes in the left VS ($p = .006$). We also investigated the relationship between the DA changes in left VS and auditory limbic pathways and found significant correlations between the DA changes and (1) rs-FC between the right posterior SFG and left hippocampus ($p = .01$) and (2) rs-FC between right Planum Polare and left amygdala ($p = .02$). However, these pathways did not correlate with the behavioral measures. Our findings suggest that auditory motor pathways may modulate motor performance and mediate the DA responses in the striatum during rhythmic auditory motor synchronization.

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Poster

497. Control of Spinal Locomotion Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 497.01/Q4

Topic: E.07. Rhythmic Motor Pattern Generation

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Title: Diversity of dopaminergic and glutamatergic marker expression in the meso-diencephalic dopaminergic nuclei in mice

Authors: *M. FOUGÈRE, D. RYCZKO;
Univ. De Sherbrooke, Sherbrooke, QC, Canada

Abstract: Dopaminergic (DA) neurons are known to use glutamate as a co-transmitter. However, whether this occurs in all meso-diencephalic DA nuclei is not fully resolved. Here, we compared the expression of DA and glutamatergic markers in A8, A9, A11 and A13 in 6 to 18 weeks old male mice. First, we carefully identified the location of A8, A9, A11 and A13 nuclei in 40 µm coronal sections of wild type mice (n = 5 mice) using immunofluorescence experiments against the tyrosine hydroxylase (TH) or the dopamine active transporter (DAT). Then, we performed the same experiments in transgenic mice expressing a fluorescent protein (ZsGreen) in neurons expressing the vesicular glutamate transporter 2 (VGluT2) (VGluT2-ZsGreen mice). For each DA nucleus, we chose a representative section and counted bilaterally the neurons positive for TH, DAT or VGluT2. Results are expressed as mean ± sem. In A8 (n = 2 mice), we found 46 ± 17 TH-positive, 43 ± 24 DAT-positive and 149 ± 35 VGluT2-positive neurons. In A9, we found 77 ± 3 TH-positive (n = 4 mice), 31 ± 20 DAT-positive (n = 3 mice) and 188 ± 24 VGluT2-positive neurons (n = 4 mice). In A11, we found 32 ± 5 TH-positive (n = 4 mice), 0 ± 0 DAT-positive (n = 2 mice) and 218 ± 14 VGluT2-positive neurons (n = 4 mice). In A13, we found 105 ± 9 TH-positive (n = 3 mice), 0 DAT-positive (n = 1 mouse) and 83 ± 17 VGluT2-positive neurons (n = 3 mice). The percentage of TH-positive cells that were also positive for VGluT2 was 99 ± 1 % in A8, 99 ± 1 % in A9, 90 ± 5 % in A11, and decreased to 1 ± 1 % in A13. Conversely, the percentage of VGluT2 cells that were also positive for TH was 30 ± 4 % in A8, 42 ± 5 % in A9, 13 ± 2 % in A11 and 2 ± 1% in A13. Our results confirm that DAT is not present in A11 and A13, whereas TH is present in the four nuclei under study. More interestingly, whereas almost no DA neuron was positive for VGluT2 in A13, almost all DA neurons in A9 were also positive for VGluT2. This suggests that meso-diencephalic DA nuclei display a clear diversity in terms of co-transmitter content, with a gradient of co-expression of dopamine and glutamate that increases from rostral to caudal DA nuclei. Whether such diversity plays a role in the variety of behaviors that DA neurons control remains to be explored.

Disclosures: M. Fougère: None. **D. Ryczko:** None.

Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: Intramural Research Program of the NIH, NINDS

Title: Stimulation of the ventral roots activates regions of the dorsal horn that are necessary to trigger locomotor-like activity in the neonatal mouse spinal cord

Authors: *M. FALGAIROLLE, M. J. O'DONOVAN;
NINDS, NIH, Bethesda, MD

Abstract: Motoneurons can trigger locomotor-like activity and regulate the frequency of the ongoing rhythm in the isolated spinal cord of the neonatal mouse. They were believed to project to only inhibitory Renshaw cells, but they have recently been shown to also target a subset of excitatory, V3 interneurons. To visualize the interneurons activated by ventral root (VR) stimulation we expressed Gcamp6f (a genetically encoded calcium indicator) into excitatory (VGLUT2-cre), inhibitory (VGAT-cre) and cholinergic (ChAT-cre) neurons, thereby encompassing the three major interneuronal classes of the neonatal mouse spinal cord (P0-P4). We focused on the caudal lumbar segments (L5-L6) whose ventral roots, when stimulated, trigger locomotor-like activity more often than the other lumbar ventral roots. We used epifluorescence to image the lateral and dorsal aspects of the cord, as well as the medial aspect of the hemisected cord and the cut transverse face (after removing the caudal or the rostral segments). Following VR-stimulation, we found that glutamatergic and inhibitory neurons were activated in the lateral deep dorsal horn, the superficial dorsal horn and along the central canal. These interneurons were tonically activated by both dorsal and VR-stimulation, were depressed in the presence of dopamine or AMPA-receptor blockade, but remained active in cholinergic antagonists. In the presence of high divalent concentrations in the extracellular solution, the VR-evoked calcium signals were enhanced even though polysynaptic components of the dorsal root-evoked responses were depressed. No calcium signals were detected in these areas when VR-stimulation failed to evoke electrical activity in other ventral roots. Partial removal of the dorsal horn in the segment of the stimulated VR, blocked activation of these regions and the locomotor rhythm. However, in these preparations, stimulation of sacral afferents could still evoke tonic calcium signals and the locomotor rhythm indicating that the locomotor circuitry was intact. Labelling and electrophysiological recordings from these neurons will be performed to determine their inputs and outputs to determine the identity of the activated cells. These results suggest that although the dorsal horn is not required for the locomotor-like rhythm, activity in dorsal interneurons appears to mediate the effects of ventral root stimulation either by amplifying the excitability of the cord or by transforming the properties of the locomotor network. This work was supported by the Intramural Research Program of the NIH, NINDS

Disclosures: **M. Falgairolle:** None. **M.J. O'Donovan:** None.

Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: Swedish Research Council (2017-02905)
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Title: Convergence and divergence of the excitatory drive to motoneurons within the spinal escape circuit in adult zebrafish

Authors: *I. PALLUCCHI[1], M. BERTUZZI[2], A. EL MANIRA[3];
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Abstract: Animals perform diverse motor actions to successfully navigate their environment. Swimming and escape are two locomotor behaviors that, in adult zebrafish, are mediated by distinct circuits. The swimming circuit comprises three speed modules, allowing a broad modulation of this behavior, making it possible to generate the locomotor rhythm and the smooth transitions in the locomotor speed. The escape circuit instead faces the necessity of ensuring a fast, strong and highly coordinated movement to avoid threats, and is mediated by activation of the fast primary motoneurons (pMNs). How the excitatory drive to the pMNs is organized within the spinal cord is still unclear. Using dual whole-cell patch-clamp recordings in the *ex-vivo* preparation of the adult zebrafish, we reveal a highly divergent connectivity pattern from a subset of dorsal V2a interneurons to pMNs. Indeed, a single escape V2a interneuron makes synaptic contact with all pMNs across several segments (up to 11 pMNs tested with a single V2a interneuron). The escape V2a interneurons are bidirectional, with a descending and an ascending axonal projection, and make synaptic connections with pMNs located both caudally and rostrally to their somata, showing a one-to-many broadcast of the synchronizing excitatory drive. The drive from a single escape V2a interneuron is shared among pMNs innervating the dorsal or ventral myotomes. Conversely, we reveal a high degree of convergence onto pMNs, with several escape V2a interneurons connected to the same pMN. These connections are mediated by mixed chemical and electrical synapses through which the state of the pMN can influence synaptic transmission. In addition, pMNs are also coupled via gap junctions, which seem to guarantee synchronization of the firing for a reliable execution of the fast and strong movement underlying escape. In conclusion, we reveal a novel circuit in the spinal cord, which contributes to the generation of the escape behavior through the excitatory drive provided by escape V2a interneurons to pMNs. Our results reveal that convergence and divergence of excitation within the spinal escape circuit ensures a powerful, synchronized output that engages fast motoneurons along the body to produce escape behavior.

Disclosures: I. Pallucchi: None. **M. Bertuzzi:** None. **A. El Manira:** None.

Poster

497. Control of Spinal Locomotion Circuits

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ControlExtraData.DynamicPosterDisplay:

Dynamic Poster

Topic: E.07. Rhythmic Motor Pattern Generation

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ERC REP-SCI-693038
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Title: Brainstem command neurons that specify locomotor direction

Authors: *J. M. CREGG, R. LEIRAS, O. KIEHN;
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Abstract: Descending command neurons instruct spinal networks to execute basic locomotor functions, such as which gait and what speed. The command functions for gait and speed are symmetric, implying that a separate unknown system with asymmetry instructs locomotor direction—left or right? Here we report the discovery that *Chx10*-lineage reticulospinal neurons act to specify the direction of mammalian locomotor movements. *Chx10* neurons exhibit exclusive ipsilateral projection, and can arrest or decrease locomotor activity ipsilaterally without affecting the opposite side. This circuit mechanism acts as the basis for left or right locomotor movements in freely moving animals: selective unilateral activation of *Chx10* neurons causes ipsilateral movements whereas inhibition causes contralateral movements. Spontaneous forward locomotion can thus be transformed into an ipsilateral movement by initiating a brake on the ipsilateral side. We identify the contralateral superior colliculus as a principal input, and show that the superior colliculus imparts directional commands via *Chx10* reticulospinal neurons. Together these data describe the only known descending system with the capacity for directing left/right locomotor asymmetries.

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Poster

497. Control of Spinal Locomotion Circuits

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Support: GLFC 54021, 54035 and 54067
CIHR 15129
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FRQS 5249

Title: The role of dopaminergic transmission in olfactomotor processing in lampreys

Authors: *P.-A. BEAUSÉJOUR[1,2], J.-C. VEILLEUX[2], F. AUCLAIR[1], S. CONDAMINE[1], G. DAGHFOUS[1], C. NGOVANDAN[1], D. VEILLEUX[1], B. ZIELINSKI[3], R. DUBUC[1,2];
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Abstract: Animals rely on chemical cues to guide locomotion towards olfactory targets such as preys and sexual partners. In the sea lamprey (*Petromyzon marinus*), a basal vertebrate, we have previously characterized a neural pathway responsible for olfactory-evoked locomotion (Derjean *et al.* 2010; PloS Biol 8(12): e10000567). The information travels from olfactory sensory neurons to a single glomerulus located in the medial part of the OB (medOB) from which projection neurons directly contact the posterior tuberculum (PT), a dopaminergic nucleus corresponding to the mammalian SNc/VTA. The PT then activates brainstem motor centers such as the mesencephalic locomotor region (MLR) and reticulospinal cells to activate spinal locomotor networks. The mechanisms by which the PT converts olfactory information from the medOB into a motor response remain undetermined.
In this study, we aimed to describe the connectivity from the medOB to the PT, notably to: (1) locate and identify the phenotype of PT neurons receiving medOB inputs, (2) describe neuronal activity generated in the PT following olfactory stimulation, and (3) investigate possible feedback mechanisms allowing the PT to modulate medOB transmission.
First, tracer injections and immunofluorescence revealed that the medOB sends abundant fibers to the PT and axons are seen close to dopaminergic, glutamatergic and GABAergic neurons co-labeled by a biocytin injection in the MLR. Moreover, multi-unit recordings revealed that several PT neurons are activated following electrical stimulation of the olfactory nerve or the medOB. Calcium imaging of PT neurons labeled with Calcium Green dextran injected in the MLR revealed different response patterns to olfactory stimulation.
We also found that dopaminergic (DA) neurons in the PT project to the medOB in addition to an intrinsic DA innervation. Intracellular recordings of reticulospinal cells displayed reduced responses to electrical stimulation of the olfactory nerve when DA was microinjected in the medOB, suggesting that DA neurons in the PT can also control the olfactory inputs they receive by modulating upstream medOB activity. Further experiments revealed that D2 and probably D1 receptors located in the medOB are involved in this modulation.
Altogether, these observations suggest that medOB projection neurons directly contact different cell populations within the PT, which then project to the MLR to drive locomotion. Moreover, DA neurons in the PT project back to the medOB providing a mechanism to gate olfactory inputs to the motor command system.

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Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: KAKENHI 26120004
KAKENHI 25290001

Title: Multi-faced functions of the reticulospinal systems involved in muscle tone regulation with respect to the modulation of neurotransmitters within the brainstem

Authors: *K. TAKAKUSAKI, M. TAKAHASHI, T. NAKAJIMA, R. CHIBA;
Asahikawa Med. Univ., Asahikawa, Japan

Abstract: The reticulospinal system is involved in state-dependent motor functions. Specifically, medullary reticulospinal neurons (RSNs), which are directly or via pontine reticular formation (PRF) neurons excited by cholinergic neurons in the pedunculopontine tegmental nucleus (PPN) are considered to induce muscular atonia during rapid eye movement (REM) sleep, while those excited by non-cholinergic neurons in the mesencephalic locomotor region (MLR) which corresponded to the dorsal part of the PPN and cuneiform nucleus are responsible for execution of locomotion during wakefulness. While not yet established, it has been hypothesized that the reticulospinal system is composed of a mixture of heterogeneous populations of RSNs having different functions, and the appropriate group of the RSNs could be selected to achieve state-dependent functions (Chase 1980). Because the PPN/MLR as well as the PRF are major targets of GABAergic, monoaminergic (noradrenergic and serotonergic), orexinergic and cholinergic systems that exhibit state-dependent alteration, here we examined how these neurotransmitter systems acting on the PPN/MLR and PRF altered the excitabilities of medullary RSNs, spinal interneurons and motoneurons innervating hindlimb muscles, resulting in modification of postural muscle tone in decerebrate cats. We observed that an activation of cholinergic PPN neurons sequentially activated cholinoceptive PRF neurons, RSNs in the dorsomedial part of the medullary reticular formation (MRF) and lumbar interneurons in the ventromedial part of the grey matter (inhibitory system) so that muscle tone was abolished. On the other hand, serotonergic projections to the PRF not only reduced the activity of the inhibitory system but excited ventromedial medullary RSNs and lumbar interneurons in the intermediate region (excitatory system), resulting in increasing the level of muscle tone. Moreover, GABAergic, monoaminergic and orexinergic projections to the PPN reduced the activity of the inhibitory system instead of increasing the activity of the excitatory system. These results suggest the presence of, at least, two sets reticulospinal-interneuronal systems with respect to the control of postural muscle tone, and either one is selected to develop state-dependent motor functions by

these neurotransmitter actions. The present findings may provide insights into the pathophysiological mechanisms of neurological disorders which associated with sleep-related motor disturbances such as narcolepsy and REM-sleep behavioral disorders.

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Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: Grant Paris-Saclay University – Strategic Research Initiatives "Project BRAINSCOPES"
ANR

Title: Endoscopic calcium imaging of brainstem V2a stop neurons

Authors: *J. SCHWENKGRUB, E. GATIER, J. BOUVIER, B. BATHELLIER;
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Abstract: Medullary V2a "stop neurons" are a genetically-defined class of brainstem reticulospinal (RS) neurons, known to regulate the episodic nature of locomotion: their controlled activation arrests locomotion by depressing rhythm-generating circuits in the spinal cord. Yet, their endogenous activity during spontaneous initiation or arrest transitions of locomotor activity has not been described. In particular, whether V2a stop neurons are transiently recruited at or prior to locomotor offset, or instead constitutively activated when animals do not walk is an important piece of information for our understanding of the neuronal coding of locomotive state.
Despite methodological advances for *in vivo* brain imaging in mice, imaging the activity of select reticulospinal circuits in freely behaving mice has remained a technical challenge owing to the deep location of neuronal somata, and the intermingling of multiple cell types in the same area. To overcome this, we first explored the efficiency of various viral vectors (different AAV constructs, HSV) to express the fluorescent calcium sensor GCaMP6 selectively in subgroups of V2a neurons defined genetically (Chx10-expressing), spatially (somatic residence) and by their projection pattern (projection to the spinal cord). We found that the most robust labelling was achieved using a Cre-dependent AAV1 injected into the medullary reticular formation of Chx10-Cre animals. Following viral injections, a gradient index (GRIN) lens was implanted above the reticular formation to enable optical access to changes of fluorescence of individual V2a neurons by epifluorescence microendoscopy. PCA-ICA algorithms as well as manual ROI selection were

applied to allow accurate cell activity detection. We identified V2a neurons whose activity was correlated with halts in locomotion and found that their mean activity is increased during non-locomotive episodes compared to ongoing locomotion, but not constitutively. With the help of machine learning, we also found that the activity of V2a RS neurons can be a reliable predictor of the transitions to locomotor arrest.
To our knowledge, no other reports have successfully targeted V2a neurons for *in vivo* imaging of reticulospinal circuit activity. Our labelling and microendoscopy methodology coupled with behavioral monitoring helps to establish a better understanding of the contributions of subcortical pathways to motor processing.

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Poster

497. Control of Spinal Locomotion Circuits

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Wallenberg Foundation (KAW 2018.0010)
Swedish Brain Foundation (FO2018-0306)

Title: Complex locomotor sequences encoded by different command neurons in adult zebrafish

Authors: *E. M. BERG, L. MROWKA, A. EL MANIRA;
Karolinska Inst., Stockholm, Sweden

Abstract: The brain is spontaneously active even in the absence of sensory inputs. Such spontaneous activity was originally thought to play a role only during early development, whereas in adults it was regarded as “noise” that needs to be overcome to allow for a meaningful information transfer. Recently, however, an emerging concept regards this activity as biologically meaningful. Here, we extend this concept to motor behavior to determine if brainstem-spinal cord circuits in adult zebrafish can generate spontaneous, versatile motor sequences in the absence of any sensory inputs. We show that the isolated CNS of adult zebrafish produces spontaneous sequences of swimming with varying vigor, i.e. fluctuations in speed and amplitude. This coordinated locomotor activity represents an internally generated correlate of spontaneous behavior in the absence of any sensory inputs. These spontaneous sequences can be of slow, less vigorous swimming activity mainly engaging slow motor units or they can spontaneously develop into motor sequences that, after a slow, less vigorous start,

switch to a fast, more vigorous activity engaging large muscle units. The onset, duration and vigor of these spontaneous swimming sequences appear to be encoded by the activity of the nucleus of the medial longitudinal fasciculus (nMLF), which is known to drive locomotion in larval zebrafish. Using patch-clamp recordings, we reveal two distinct subtypes of neurons in the nMLF that selectively encode the different aspects of the spontaneous swimming sequences. The first subtype, which is located medially in the nMLF, encodes the onset and duration of the swim sequence and is active during slow, less vigorous swimming. The second subtype, located laterally, encodes the increase of vigor and becomes active during the transition to faster and stronger swimming of a spontaneous sequence. These two subtypes of nMLF neurons are spatially segregated and appear to receive inputs from different brain areas. In summary, we show that complex motor sequences are generated intrinsically in the absence of any sensory input and their onset, duration and vigor are encoded by specific midbrain command neurons.

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Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

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Title: Serotonergic neurons involved in the excitation of spinal neurons

Authors: *K. E. ARMSTRONG[1], S. BHAYVA[1], M. NAZZAL[1,2], X. CHEN[1], U. SLAWINSKA[2], K. STECINA[1], L. M. JORDAN[1];
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Abstract: Different effects of $5HT_7$ receptor blockade on limb coordination in the neonatal and adult rats suggests that there may be major developmental changes in the influence of 5-HT on locomotion. Previous research has determined that electrically stimulating the parapyramidal region (PPR) in neonatal rats can initiate locomotor-like activity and the presumed mechanism of action is serotonergic (5-HT) as using a $5\text{-}HT_7$ receptor antagonist applied on the surface of the lumbar cord blocked the evoked locomotor-like activity. Similarly, the blockade of the $5HT_7$ receptors in adult rats can also halt fictive locomotion, but not over ground locomotion.

The aims of this study were to determine the changes during development of spinal 5-HT_7 receptors and the contribution of serotonergic neurons to the initiation or the facilitation of locomotion in adult rodents. The protein expression levels of 5-HT_7R were detected in different spinal segments in 3, 6,15 day old rats and adults (n=4-5/group) using Western Blot. For the selective excitation of 5-HT neurons, excitatory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs, n=9) were stereotaxically injected into the PPR using adeno-associated viral vectors (AAV8-hSyn-DIO-hM3Dq) in adult female rats with Cre-recombinase in 5-HT neurons. After a recovery period experiments were performed in decerebrated (un-anesthetized) rats while recording lumbar ENG activity and arterial blood pressure. Mesencephalic locomotor region stimulation was used to induce fictive locomotor activity in order to assess changes after applying the DREADD actuator clozapine-N-oxide (CNO) via intracerebral (i.c.) injections. The injection site was verified post-hoc with frozen-sectioned tissue by mapping the DREADD fluorescent reporter protein. Aged matched, non-injected female rats were a used as controls (n=8). We examined changes in fictive locomotor output and BP responses. We found changes in $5HT_7$ receptor expression levels in multiple spinal regions over the age groups tested, with the lumbar cord showing a highly significant downregulation in adults when compared to younger rats. Our previous research (Armstrong et al., SFN 2017) used systemic injections of CNO, but it is now known that CNO metabolizes to clozapine, and clozapine can negatively influence the locomotor networks. By using i.c. injections, we have found that potential for back metabolism is reduced and we have more robust changes to both fictive locomotion and blood pressure after i.c. application of CNO. The i.c. injections of saline had no effect on the amplitude or frequency of BP or ENG output.

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Poster

497. Control of Spinal Locomotion Circuits

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Program #/Poster #: 497.10/Q13

Topic: E.07. Rhythmic Motor Pattern Generation

Support: NIH U01NS103489

Title: Neuronal age-related recruitment and coordination among reticulospinal neurons control stimulus-dependent variability of escape behavior in larval zebrafish

Authors: M. TANIMOTO[1], *A. PUJALA[2], R. LU[3], N. JI[4], M. KOYAMA[1];
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Abstract: Reticulospinal (RS) neurons control various aspects of locomotion such as its initiation, duration, and termination. However, we understand little of how the activity is coordinated among RS neurons to produce a flexible locomotor repertoire. We chose to address this question in the context of escape behavior in larval zebrafish. During escape, a zebrafish transitions from fast whole-body movements to slower movements of the caudal part of the tail. As both the fast and slow phases display inherent and stimulus-dependent variability (Liu and Fetcho, 1999; Pujala and Koyama, 2019), escape provides an opportunity to examine the coordination of RS neurons and its role in behavior. We first examined Ca^{2+} responses of RS neurons with 2-photon Bessel beam imaging while delivering electrical stimuli either to the head or tail to induce variable escape responses. Behavior was monitored either with video monitoring of tail movements in head-fixed preparations or with EMG recordings of axial muscles in genetically paralyzed fish. This revealed distinct recruitment of RS neurons based on their differentiation time similar to hindbrain V2a neurons (Pujala and Koyama, 2019). Short-latency response was almost always accompanied by activation of the Mauthner cell, which is the earliest born neuron within the RS group. The activity of several other early-born neurons was modulated based on the strength of the fast phase of escape response. On the other hand, the activity of later-born neurons was dependent on the duration of the slow phase of escape. Loose-patch recordings further revealed that many neurons within the early-born group exhibit transient spiking only when fish exhibit strong movements during the fast phase of escape, whereas the later-born group exhibits spiking that is sustained until the end of the slow phase. Femtosecond laser ablations of each of these groups revealed their causal contributions towards a specific phase of the escape response: the early-born group contributes to the fast phase while the later-born group contributes to the slow phase. Preliminary single-cell labeling and paired recordings of RS neurons revealed spinal connectivity patterns consistent with a phase-specific role for each age group. Taken together, these analyses revealed temporally coordinated recruitment of distinct age groups of RS neurons, each of which contributes to flexibility within a particular phase of escape behavior. Moreover, these results opened a way to study the detailed circuit mechanisms of how neurons born at different times are coordinated together to produce coherent behaviors.

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Poster

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H.A. and Mary Chapman Charitable Trust
Bert and Ethel Aginsky Research Scholar Award

Title: Exploring inhibitory neuronal connectivity in the mouse locomotor circuit

Authors: *S. DI COSTANZO[1,2], G. GATTO[1], F. STAM[1], M. GOULDING[1];
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Abstract: Terrestrial vertebrate animals generate a wide array of locomotor behaviors that rely on the timely coordination of flexor-extensor muscle activity across several joints to generate limb movement. This coordination is finely regulated by a core network of spinal cord interneurons (INs) defined as the locomotor central pattern generator (CPG). Previous studies from our laboratory found that two inhibitory IN populations within the CPG network, defined as V1 and V2b INs based on their developmental origin, regulate flexor-extensor motor activity during different phases of the walking step cycle. V1 INs control locomotor speed and suppress flexor activity during extension in the stance phase of walking, whereas V2b INs suppress extensor activity during the swing phase of walking. This evidence led us to ask whether this differential contribution to locomotion is determined by a distinct recruitment of these two classes of INs during walking. Thus, we decided to investigate the spinal and peripheral monosynaptic inputs onto V1 and V2b INs. We have used a combination of mouse genetics and viral rabies-based tools to perform an accurate anatomical analysis of their respective connectivity patterns. This involved the generation of a double stop mouse line to restrict the TVA receptor and the G protein expression to neurons expressing both *Cre* and *FlpO* recombinases. Using specific intersectional genetic tools, we were able to selectively infect V1 and V2b INs with an EnvA pseudotyped rabies virus. Interestingly, our results indicate that these two IN populations receive partially differential inputs from the local spinal circuit and from DRG afferents. So far, our data confirms the hypothesis that, while these two inhibitory IN populations encompass partially overlapping functional cell types, their differential connectivity to the spinal cord/DRG microcircuitry suggests they might be differentially recruited during the step cycle. By studying the anatomical connectivity of V1 and V2b neuronal circuits, we aim to clarify how the activity of individual inhibitory population help shape movement and how CPG INs integrate external cues from the environment, which is still largely unknown.

Disclosures: S. Di Costanzo: None. **G. Gatto:** None. **F. Stam:** None. **M. Goulding:** None.

Poster

497. Control of Spinal Locomotion Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 497.12/Q15

Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR
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NSHRF

Title: Spinal V3 Interneuron subpopulations diversify along temporally ordered developmental pathways

Authors: *D. A. DESKA-GAUTHIER[1], J. BOROWSKA-FIELDING[1], H. ZHANG[1], J. B. BIKOFF[3], Y. ZHANG[2];
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Abstract: Animals exhibit a wide range of locomotor behaviours empowering their navigation through dynamic environments across land, sea and air. Spinal interneurons (INs) form the basic sensorimotor circuits that ensure coordinated spatiotemporal muscle contractions from leisurely walking, to high-speed running, to swimming. However, the functional architecture and heterogeneity of spinal IN circuits underlying their control of task-dependent locomotor outputs remains largely elusive. In the current work, through investigation of the cardinal V3 IN population, we reveal that molecularly discrete V3 subpopulations diversify along temporally-ordered early embryonic timelines forming heterogeneous laminar clusters, axon projection profiles, sensory innervations, and intrinsic electrophysiological and morphological properties. Furthermore, through an investigation of task-specific c-fos expression, we revealed that molecularly discrete dorsal V3 subpopulations are differentially recruited across distinct speed- and weight bearing-dependent sensorimotor behaviours. Thus, our current work indicates that developmentally and genetically discrete IN subpopulations are the building blocks of topographically clustered spinal circuits engaged across different locomotor tasks.

Disclosures: D.A. Deska-Gauthier: None. **J. Borowska-Fielding:** None. **H. Zhang:** None. **J.B. Bikoff:** None. **Y. Zhang:** None.

Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: ANR
Region Ile de France DIM
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Title: Distinct neuronal drives from central locomotor circuits modulate breathing during exercise

Authors: *C. HÉRENT, S. DIEM, G. FORTIN, J. BOUVIER;
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Abstract: When animals run, respiration increases to match the augmented energetic demand. Yet the neuronal bases of this homeostatic adjustment are poorly documented. Here we investigated, in mice, i) the nature of respiratory changes during acute locomotor exercise, ii) the possibility that central locomotor circuits directly modulate breathing, and iii) the identities of putative respiratory neuronal targets.
First, we combined chronic electromyographic recordings of the diaphragm with limb video-tracking in mice running on a treadmill and show that the breathing frequency increases immediately at the onset of locomotion. This operates without temporal coupling of the locomotor and respiratory rhythms, regardless of the locomotor speed and gait. We next addressed the possibility that the mesencephalic locomotor region (MLR), enabling locomotor initiation, may in addition modulate breathing. We show that photo-activation of glutamatergic MLR neurons can reset the respiratory rhythm and upregulates breathing frequency prior to locomotor movements. Since the respiratory frequency then further increases upon locomotor engagement, we also investigated a possible direct influence of the spinal locomotor central pattern generator (CPG) on respiratory activity using *ex-vivo* brainstem/spinal-cord preparations from neonatal mice. We find that activating the locomotor CPG increases the frequency of inspiratory-like activity.
Viral tracings indicate that the MLR sends collateral projections to the preBötzinger complex (preBötC), the main inspiratory rhythm-generator, while the locomotor CPG does not but rather targets the Retro-Trapezoid Nucleus (RTN), another essential population of respiratory neurons. Accordingly, genetic-deletion or chemical-silencing of RTN neurons, respectively *ex-vivo* and *in-vivo*, reduces the locomotion-induced respiratory increase.
Altogether, our work indicates that central locomotor circuits provide distinct drives to respiratory centers: 1) a descending feedforward drive from the MLR to the preBötC that may prime respiration in anticipation of exercise and 2) an ascending drive from the locomotor CPG to the RTN that increases respiratory frequencies during ongoing locomotion.

Disclosures: C. Hérent: None. **S. Diem:** None. **G. Fortin:** None. **J. Bouvier:** None.

Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

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Title: Functional organization of the spinal locomotor network based on analysis of interneuronal activity

Authors: *P. V. ZELENIN[1], O. V. GORSKII[2], Y. P. GERASIMENKO[2], T. G. DELIAGINA[1], P. E. MUSIENKO[3];
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Abstract: In vertebrates including humans, the basic pattern of locomotor movements is generated by a neuronal network residing in the spinal cord (the spinal locomotor network, SLN), while the descending commands from the brain turn SLN on and off, control the vigor of locomotion, modify the basic pattern for steering, obstacle avoidance, etc. Forward locomotion can be evoked and its vigor can be controlled in the decerebrate preparation by stimulation of the mesencephalic locomotor region (MLR) of the brainstem. This experimental paradigm has been extensively used for investigation of SLN. However, due to technical difficulties related to recording of spinal interneurons during real locomotor movements, the experimental data related to operation of SLR during real locomotion with normal sensory feedback are extremely limited, and the majority of data were obtained during fictive locomotion in the paralyzed animals. In the present work, we managed to overcome technical problems and to record activity of putative spinal interneurons from L4-L6 during real MLR-evoked treadmill locomotion with normal sensory feedback in the decerebrate cat preparation. We analyzed their activity phases by taking into account the previously ignored information about stability of neuronal modulation in the sequential locomotor cycles. First, data with smaller variability are more reliable statistically per se. Second, one can suppose that interneurons constituting the SLN core, have more stable activity than those receiving locomotion-related input but not critically important for generation of locomotor movements. Our analysis allowed to reveal functional neuronal groups presumably generating the vertical and horizontal components of the step, and to characterize their location in the spinal cord. Based on analysis of the relationship between activity phases of the groups, we suggest functional connections between them and propose a novel model for generation of locomotion that combines the reciprocally active half-centers with the generating ring.

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Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

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Title: A model for self-organizing spinal cord circuitry through learning

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Abstract: In order to test the feasibility of self-organization in the spinal cord based on musculoskeletal mechanics and behavioral experience, we have designed a model creature with the simplest musculoskeletal system and sensor population that we thought might exhibit an interesting range of behaviors. The nervous system is composed of simplified, non-spiking neurons with linear transfer function and implementing a variant of Hebbian learning. We describe how randomly activated movement patterns such as generated in early development could give rise to naturally occurring connectivity patterns between sensors and spinal neurons. These are the first steps toward identifying how the CNS could potentially discover and utilize such adaptive mechanisms to help shape spinal circuits that ultimately facilitate the learning and performance of voluntary behaviors.

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Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: CIHR MOP 86470

CFI AET
Stollery Children's Hospital Foundation/Women and Children's Health Research Institute
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Title: Analysis of the transverse distribution of the locomotor CPG during different speeds of fictive locomotion

Authors: V. RANCIC, K. BALLANYI, *S. GOSGNACH;
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Abstract: The basic rhythmic activity that underlies stepping is generated by a neural network, situated in the spinal cord, known as the locomotor central pattern generator (CPG). While a series of lesion experiments has demonstrated that the mammalian locomotor CPG is distributed throughout the lower thoracic and lumbar spinal cord, the specific transverse distribution of the component interneurons that comprise this neural network is unclear. Here we use an isolated, upright spinal cord preparation and evoke fictive locomotor activity of various frequencies either by electrical stimulation of the brainstem, or by the application of a series of pharmacological cocktails. This preparation enables us to identify locomotor-related neurons across the transverse plane of the spinal cord by discerning all those neurons that exhibit rhythmic Ca^{2+} oscillations which have the same frequency as electroneurogram activity recorded from the hindlimb ventral roots. Analysis of preliminary data indicates that locomotor-related interneurons are distributed throughout the ventral spinal cord with the majority located ventromedially. Interestingly, the specific neurons that are rhythmically active, and the overall pattern of activity observed, changes when the speed of fictive locomotion is altered. These findings are consistent with data indicating that there is a speed dependent recruitment of interneuronal populations during locomotion, and suggests that the locomotor CPG is not a static network, but rather the specific neurons recruited vary extensively based on demand.

Disclosures: V. Rancic: None. **K. Ballanyi:** None. **S. Gosgnach:** None.

Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

Support: NSERC RGPIN-2016-03790
Fonds de Recherche du Québec 182035
NIH R01NS090919

Title: Cats stepping on a split belt treadmill reveal a functional organization of commissural interactions within the spinal locomotor circuits

Authors: E. M. LATASH[1], W. H. BARNETT[1], R. A. CAPPS[2], S. M. DANNER[4], A. FRIGON[5], I. A. RYBAK[4], *Y. I. MOLKOV[3];
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Abstract: Rhythmic limb movements during locomotion are controlled by oscillatory neural networks/central pattern generators (CPGs) located in the spinal cord. It is considered that a separate CPG controls each limb. Dynamic interactions between CPG networks coordinate left and right limbs during locomotion. These interactions have been experimentally investigated using spinalized cats stepping on a split-belt treadmill. The speed of each belt was varied in a tied-belt or split-belt fashion while recording continuous gait transformations. In tied-belt experiments with increasing belt speed, swing phase duration remained relatively constant, whereas stance phase duration decreased. In this case, the gait represented a symmetric antiphase pattern, in which the swing phases of left and right legs were separated by intervals of dual support when both limbs were on the ground. In split-belt experiments, the locomotor pattern was perturbed asymmetrically. At low ratios of belt speeds, stance duration on the fast side decreased but cycle duration remained the same bilaterally. At high ratios of belt speeds, the cats produced multiple steps on the fast side for each step on the slow side. Split-belt experiments also revealed an asymmetric mode of synchronization in which stance on the slow side was initiated when stance on the fast side ended. Thus, the swing phase on the fast side immediately succeeded swing on the slow side without an interceding interval of dual support.We adopted these experimental results to elucidate potential neuronal mechanisms of interlimb coordination using a tractable mathematical model describing two interacting locomotor CPGs controlling left and right limb oscillations. Each CPG contained two neuronal populations mutually inhibiting each other representing flexor and extensor CPG half-centers. A slowly inactivating persistent sodium current governed dynamics of rhythmic activity in both neuron populations and neuronal synchronization within each population. An excitatory drive to the flexor population defined the oscillation frequency of each CPG and each flexor population received commissural inhibitory inputs from the contralateral flexor and extensor populations. We simulated split-belt locomotion by setting different oscillation frequencies in left and right CPGs. By analyzing model behavior under different conditions, we identified dynamic properties of the CPGs and organization of commissural interactions between them, allowing the model to reproduce experimental data on tied-belt and split-belt locomotion. Our results reveal an organization of commissural interactions within spinal locomotor circuits.

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Poster

497. Control of Spinal Locomotion Circuits

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Topic: E.07. Rhythmic Motor Pattern Generation

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CIHR Grant MOP110950

Title: Role of spinal V3 interneurons in left-right coordination of locomotor activity

Authors: N. A. SHEVTSOVA[1], H. ZHANG[2], S. DANNER[1], I. RYBAK[1], Y. ZHANG[2];
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Abstract: Left-right coordination during mammalian locomotion is provided by several types of commissural interneurons (CINs) that mediate interactions between rhythm generating circuits located on each side of the spinal cord. It has been shown that alternation of left and right rhythmic activity in the cord involves V0 CINs. While V3 CINs have been implicated in left-right coordination, the mechanisms by which they interact with the spinal rhythm generators and regulate the locomotor activity remain elusive. To address this issue, we combined experimental studies with computational modeling. Fictive locomotor activity was evoked by NMDA/5-HT mixture in the isolated neonatal spinal cord of *Sim1*$^{Cre/+}$*; Rosa 26*$^{ChR2(H134R)-EYFP}$ mice, in which V3 interneurons could be photo-activated. Flexor and extensor activities were recorded from left and right L2 and L5 ventral roots, respectively. Bilateral photoactivation of V3 neurons slowed down the ongoing rhythm, prolonged extensor phase durations, increased the extensor burst amplitude, and, at high light intensities, could stop rhythmic activity. When photostimulation of V3 neurons was applied to one side of the cord, the locomotor cycle period and extensor burst durations on both sides were increased, but the degree of changes on the contralateral side was more significant than on the ipsilateral side. Further increase of the stimulation could eventually suppress the contralateral oscillations with a sustained extensor activity, while the ipsilateral rhythmic activity remained. To further delineate the V3 function, we developed a computational model of the spinal circuits consisting of two (left and right) rhythm generators (RGs) interacting via $V0_V$, $V0_D$ and V3 CINs. With the suggestion that V3 CINs provide mutual excitation between the left and right RG's extensor centers, the model was able to reproduce our experimental data described above. Additionally, the model was consistent with the well-established function of V0 CINs as the regulators of left-right alternation during locomotion,

which further validated our model. Based on the combined experimental and modeling studies, we suggest that V3 CINs provide mutual excitation between the left and right extensor centers.

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Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.01/R4

Topic: F.01. Neuroethology

Title: Correlating neural and behavioral responses in an insect model

Authors: *B. A. NAVIA, B. SHIN;
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Abstract: Phonotaxis in female cricket *Acheta domesticus* can be selective or unselective in response to model calls with varying syllable periods. Discrimination of and movement towards a model call implies that networks of neurons are activated when the call is recognized as attractive. Several approaches to demonstrate the influential role of auditory neurons in phonotaxis have been used with different levels of success. One such approach (current study) seeks to evaluate the behavioral and neuronal responses in the same animal, using identical auditory stimuli. This approach allows us to establish a correlation between the neuronal and behavioral responses, as well as to predict the behavior of the animal based on the response of an auditory neuron. A number of auditory neurons (in the brain and prothoracic ganglion) in this model have been identified and proposed to play a role in the control of phonotaxis. The L3 prothoracic auditory neuron has been suggested to influence syllable period selective phonotaxis in this species. In response to calls with attractive syllable periods, the L3 produces a burst of action potentials, which diminish in response to consecutive syllables. Such a decrease in the number of action potentials calculated as percentage is called decrement. Preliminary results indicate that syllable periods which produce positive phonotaxis, also elicit higher decrement values in the neuronal response of the same animal. In the lab, young (5-10 days), virgin females are more likely to respond phonotactically to calls with syllable period ranging between 50 and 70 ms. Older, virgin females (> 20 days), exhibit more variability in the range and number of syllable periods they respond to, which may or may not overlap with the range indicated for young ones. Implications of these findings are discussed.

Disclosures: **B.A. Navia:** None. **B. Shin:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

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Program #/Poster #: 498.02/R5

Topic: F.01. Neuroethology

Support: NIH SC2DA034996
NSF IOS-1456743
NSF IOS-1456700

Title: Testosterone levels regulate dopamine innervation in the inner ear of a seasonally breeding vocal fish

Authors: *J. PERELMUTER[1], L. DEMIS[2], R. A. MOHR[3], J. A. SISNEROS[4], P. M. FORLANO[5];
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Abstract: Seasonally breeding vertebrates often undergo dramatic changes to sensory systems, facilitating the detection and evaluation of mates during courtship, however the mechanisms regulating these changes are not well understood. The plainfin midshipman (Porichthys notatus) is a marine teleost that migrates from deep water winter habitats to coastal breeding sites in the summer. Courting males use acoustic signals to attract females to their nests. Coincident with the transition from nonreproductive to reproductive state, females undergo both an increase in peripheral auditory sensitivity and a decrease in dopaminergic efferent innervation of the inner ear. Previous work has linked changes in gonadal hormone levels, including testosterone, to peripheral auditory plasticity. Furthermore, we have recently demonstrated that the summer reduction of dopamine in the inner ear results in a release of inhibition, contributing to the adaptive increase in auditory sensitivity. To determine if testosterone regulates dopamine, we ovariectomized nonreproductive, winter females and treated them with either testosterone or control elastomer implants and, after a 30-day period, assessed both circulating testosterone levels and dopamine innervation in the inner ear via immunohistochemical labeling with tyrosine hydroxylase (TH) antibodies. In the experimental group, testosterone levels were elevated and negatively correlated with the number of TH puncta (putative release sites of dopamine). These data support the hypothesis that a pre-migration increase in testosterone initiates the seasonal change to dopamine input to the inner ear, which directly alters peripheral auditory sensitivity. Androgenic regulation of dopamine may be a mechanism by which other seasonally breeding vertebrates synchronize reproductive readiness and nervous system plasticity.

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Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.03/R6

Topic: F.01. Neuroethology

Support: NSF IOS 1557945

Title: Molecular characterization of vocal neurons in Xenopus laevis

Authors: R. T. INAGAKI[1], S. RAGHURAMAN[1], L. LEAVITT[1], K. CHASE[1], T. STEEL[2], E. ZORNIK[2], B. M. OLIVERA[1], ***A. YAMAGUCHI**[1];
[1]Sch. of Biol. Sci., Univ. of Utah, Salt Lake City, UT; [2]Biol., Reed Col., Portland, OR

Abstract: A major goal of neuroscience is to understand the neural mechanisms of behavior. We have focused on the central vocal pathways of African clawed frogs (Xenopus laevis) to address this question because of the simplicity of its sound generating mechanism and the availability of fictive vocalizations that allow us to study the neuronal activity underlying behavior *in vitro*. Previously, we have identified a type of premotor neuron called Fast Trill Neurons (FTNs) in the central vocal pathways of the X. laevis, that are critical for vocal production in males. Previous electrophysiological studies showed that the FTNs express NMDA receptors and GABA/Glycine receptors. Molecular characterization of different types of neurons provide a foundation for discovering the functional role of each cell type in the circuit. In this study, we further explored additional molecules that are expressed by the FTNs in order to better predict the functional properties of the neurons. To this end, we used constellation pharmacology and single-cell RNA sequencing to characterize FTNs. Constellation pharmacology is a cell-based high-throughput phenotype-screening method that utilizes pharmacological agents to illuminate the cell-specific combination (constellation) of key proteins such as ion channels and receptors that define specific cell types. The technique involves imaging intracellular Ca^{2+} levels in >500 neurons in primary cell culture and monitoring neuronal response to a battery of ligands. Thus, the Ca^{2+} response profile generated by every neuron allows the identification of unique combinations of receptors and ion channels expressed by different neuronal cell types. Using this technique, we identified four classes of putative FTNs. In addition to their sensitivity to NMDA and GABA/glycine, these four classes of neurons showed sensitivity to substance P and/or ACh. Intracellular recordings obtained from FTNs using a whole-brain preparation verified that the neurons depolarize in response to substance P and/or ACh. In addition to these receptors, we have carried out single-cell RNA sequencing following the constellation pharmacology to

identify transcripts expressed by the FTNs. The identification of key proteins expressed by FTNs allows us to deduce the function of the neuron.

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Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.04/R7

Topic: F.01. Neuroethology

Support: Israeli Science Foundation
Gatsby Charitable Foundation

Title: Syntax information maximization: Optimizing classification of mouse ultrasonic vocalizations

Authors: ***S. HERTZ**, B. WEINER, N. PERETS, M. LONDON;
The Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Vocal communication in animals is a prevalent behavior with practical implications for understanding the neural control of speech. Rodents are an attractive animal model for this purpose, but understanding their ultrasonic vocalizations (USV) is limited because we do not know the basic building blocks and their rules of assembly. Many algorithms for classifying USVs into syllables based on their individual acoustic features are constantly being developed, but there is currently no objective criterion to evaluate the quality of their results.
Here, we developed a statistical framework based on information theory (named Syntax Information Score, SIS) that allows comparison and ranking of arbitrary classification algorithms of sequential data. We further designed and tested a novel algorithm (Syntax Information Maximization, SIM) that showed that the SIS can be used to optimize the classification of USVs. To support the statistical framework, we composed a dataset by recording USVs during male-female interaction sessions (460,000 USVs grouped into 44,000 sequences). We used this dataset to compare the classifications of three popular algorithms. The statistical comparison showed that the classifications were fundamentally different and nonhomologous. In addition, Markov model analysis of the labeled USV sequences revealed high-order structures (i.e., syntax), with the label of a USV dependent on the labels of preceding USVs. As the Markov models differed between the algorithms, we developed the Syntax Information Score (SIS) that provides a quantitative comparison of classifications based on their predictive power. The SIS was used to measure the capabilities of the three algorithms to find regularities in the data. Finally, we designed and tested the Syntax Information Maximization (SIM) algorithm. The SIM

incorporates optimization of the predictive power as an integral driving force of a classification algorithm. We applied the SIM on a training-set of USV sequences, and showed that it was able to generalize to data that had not been considered before (the test-set), resulting with an improved classification of USVs.
Improvement in USV classification is crucial for interpreting social interactions, and for understanding neural control of vocalization. Our results demonstrate that USV syntax holds valuable information for achieving this goal.

Disclosures: **S. Hertz:** None. **B. Weiner:** None. **N. Perets:** None. **M. London:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.05/R8

Topic: F.01. Neuroethology

Title: Using a sound source localization system to determine the function of mouse vocal signals during naturalistic group interaction

Authors: *M. R. WARREN, R. S. CLEIN, J. P. NEUNUEBEL;
Univ. of Delaware, Newark, DE

Abstract: Across the animal kingdom, acoustic communication is vital for transferring information between animals, conveying social status, reproductive interest, and kinship [Bradbury and Vehrencamp, 2011; Matsumoto et al., 2016; Moles et al., 2007]. Similar to other animals, mice vocalize in a myriad of social contexts [Kazdoba et al., 2016] and have therefore become a valuable model to study vocal communication [Burke et al., 2018]. There is, however, a lack of detailed knowledge about the information communicated between mice and how vocal signals shape social behavior. This is due to difficulties in identifying the vocal activity of specific individuals within social groups. We overcame this difficulty by employing an eight-channel microphone array system to track the vocal activity of individual mice within groups [Warren et al., 2018]. We discovered that mice emit specific types of vocal signals based upon their role in a social encounter: males acting aggressively typically emit signals that decrease in frequency, while males acting submissively emit signals that increase in frequency. While the results indicate that mice emit behaviorally-dependent vocalizations, we have been unable to determine the role these signals may play in shaping social behavior Therefore, to identify the function of signal emission, we used a conditional mouse model of deafness (B6.Pou4f3tm1.1; [Tong et al., 2011]) to selectively ablate hearing in adults (8-12 weeks) and, consequently, sever the flow of auditory information between animals. Genotype-matched groups of four mice (two males and two females), either hearing (WT; n = 6 groups) or conditionally deafened (Het; n = 6 groups), were allowed to freely interact over 5 hours. We found that hearing and deafened mice

engaged in similar numbers of social behaviors, including males following other males (Mann-Whitney; $Z = -0.75$, $p = 0.45$), males following females ($Z = 0.85$, $p = 0.58$), and males fleeing from other males ($Z = 0.66$, $p = 0.51$). When assessing context-dependent vocal emission, hearing mice replicated our previous findings, altering their vocal repertoire based upon behavioral context. Strikingly, deafened males also emitted context-dependent vocal signals. This novel finding, in conjunction with our ability to track the instantaneous behavior of multiple mice simultaneously, will allow us to determine the immediate behavioral response to these signals as a function of hearing ability. This will provide vital information about the role vocal signals play in mouse communication as well as the extent to which these signals communicate social information.

Disclosures: **M.R. Warren:** None. **R.S. Clein:** None. **J.P. Neunuebel:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.06/R9

Topic: F.01. Neuroethology

Title: Quantifying dynamic social and vocal behavior of freely interacting mice using a sound source localization system

Authors: *R. S. CLEIN[1], D. T. SANGIAMO[1], M. R. WARREN[1], J. P. NEUNUEBEL[2]; [2]Psychological and Brain Sci., [1]Univ. of Delaware, Newark, DE

Abstract: Across the animal kingdom, social status affects access to the resources necessary for survival and reproductive success. Social status is determined by the outcome of agonistic behaviors and stabilizes over time (Williamson et al., 2017). In mice, most studies examining social dominance focus on interactions that occur when hierarchical relationships are stable. However, a detailed understanding about the development of hierarchical relationships is lacking. We recorded unrestricted social interaction in mixed-sex (2 males and 2 females) groups ($n = 11$) of adult mice (B6.CAST-Cdh23Ahl+/Kjn, 13-21 weeks old). Interactions were recorded for 5 hours using a sound source localization system (Warren et al., 2018), and then courtship and agonistic behaviors were automatically extracted with a machine based learning system (Kabra et al., 2013). To quantify social status, we calculated a step function based on when male-male agonistic behaviors occurred. Each function allowed us to define discrete behavioral states where one male was engaging in all of the agonistic or submissive behaviors. Using these functions, we quantified the number of times that the aggressor changed (state changes), and the magnitude of the overall difference in social status. Across experiments, the number of state changes (14-125) and the overall difference in status (absolute values: 0.02-0.97) were negatively correlated ($r = -0.68$, $p = 0.02$). When examining how social status affected the

interactions between a male and female, we found that the male's overall status was not predictive of the number of courtship displays ($p = 0.10$) or propensity to interact with females immediately following an aggressive behavior ($p = 0.65$). Interestingly, a male's current behavioral state influenced his courtship displays. Males in an aggressive state engaged in more courtship chases than males in a submissive state ($p = 0.03$). Males in a submissive state, however, had a greater propensity to immediately interact with females following agonistic behaviors than their aggressive counterparts ($p < 0.01$). Additionally, submissive males vocalized more than aggressive males during the social interactions with females ($p = 0.02$). Taken together, these results suggest that a male's particular role in a recent agonistic experience impacts subsequent interactions with a female.

Disclosures: R.S. Clein: None. **D.T. Sangiamo:** None. **M.R. Warren:** None. **J.P. Neunuebel:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.07/R10

Topic: F.01. Neuroethology

Support: Independent research fund Denmark

Title: Mechanisms of ultrasonic vocalization production in excised rat larynges

Authors: *J. HÅKANSSON[1], A. AGARWAL[2], C. P. ELEMANS[1];
[1]Univ. of Southern Denmark, Odense M, Denmark; [2]Dept. of Engin., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Murine rodents produce ultrasonic vocalizations (USVs; pitch ranging from 30 to 100 kHz) that play important social roles, such as mating and territorial defense. Furthermore, pup USVs are crucial to induce maternal search and retrieval behavior, while visual or olfactory cues are less relevant. Because USVs in rodents do not appear to be learned, they have become a vital and rapidly increasingly used translational tool for linking gene mutations to behavior in mouse and rat models of neurodevelopmental, communication, and autism spectrum disorders. These genetic models demonstrate significant acoustic changes that resemble the atypical vocalizations seen in human disorders. However, we cannot meaningfully relate acoustic features to experimental treatments or rodent models, because we have a critical lack of insight into which physical and physiological mechanisms of USVs are produced and controlled by the brain and which result from potential changes to the larynx physiology. To test the current outstanding hypotheses on how laryngeal morphology contributes to USV production in rats, we combined *in vitro* excised larynx experiments with computational flow models. USVs were produced only

when the arytenoids and vocal folds were opposed, leaving only a small opening at the dorsal region of the vocal folds, close to the arytenoid cartilages, which is consistent with *in vivo* endoscopic observations. Additionally, larynges were fixed in specific USV producing configurations and their 3D geometries were quantified from microCT scans. We then simulated fluid flow though the 3D geometries to estimate crucial control parameters of whistle frequencies. Furthermore, we tested the importance of the ventral pouch on rat USV production by experimental manipulations and showed larynges capable of producing USVs without air flow jet hitting the alar edge and resonating the ventral pouch.

Disclosures: J. Håkansson: None. **C.P. Elemans:** None. **A. Agarwal:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.08/R11

Topic: F.01. Neuroethology

Title: Take a deep breath: Sighing and vocal motor control in SD-rats

Authors: *T. RIEDE;
Midwestern Univ., Glendale, AZ

Abstract: Augmented breathing or sighing is a characteristic breathing pattern in rodents generated by dedicated midbrain neuron populations. Its main function is to prevent alveolar collapse, but in some species, most prominently in humans, augmented breaths are incorporated into vocal behavior. A role of augmented breathing for vocal production in other mammals is unknown. Here we utilize subglottal pressure recording in awake spontaneously behaving male Sprague Dawley rats to elucidate the role of augmented breaths in ultrasonic vocalization. Overall breathing rate is dependent on social context or motor activity. We found that sighing rate did not change in different contexts. Furthermore, rats place vocalizations into more than one fifth of their augmented breaths ("vocal sighing") during social interactions. Different call types and sometimes multiple calls were placed into the exhalation phase following an augmented inhalation. The exhalation phase changed in a call type specific manner. We also found differences in the shape of the augmented inhalation pressure signal preceding a vocal sigh. We conclude that vocal motor control is integrated with sighing behavior.

Disclosures: T. Riede: None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.09/R12

Topic: F.01. Neuroethology

Support: NIH Grant R15 MH117611-01A1

Title: Using degus to studying relationship formation between adult females

Authors: A. L. THATCHER, S. COOKE, K. WEBB, K. BUTLER, *N. INSEL;
Univ. of Montana, Missoula, MT

Abstract: Many animals form long-term social bonds that allow them to coordinate and cooperate with one another. In mammals, cooperative and affiliative behaviors are particularly common in females; for example, in degus (a rodent native to South America), unrelated females share burrows, nurse each-other's young, and show coordinated behaviors during digging and foraging. The process by which initial strangers come to learn about one-another to coordinate their behavior is not well understood. To study the behavioral dynamics of this learning, and thereby gain insight into the processes that allow animals to learn about one-another over time, we examined interactions between strangers over a sequence of multiple, "reunion" social exposures. Pairs of female degus were exposed separately to stranger and cagemate conspecifics for 20 min periods, with each exposure taking place once every other day over a 20 day period. Strangers were then co-housed for 24 hours, followed by two additional exposures of pairings with these "new cagemate" dyads and, separately, with new strangers. We found that strangers showed more interactions than cagemates, including more anogenital sniffing, agonistic behaviors, and face-to-face encounters. Unexpectedly, however, these differences persisted over multiple sessions, including after the 24 hour cohabitation period. Continued analyses are examining whether interaction patterns are unique to each dyad, and whether these change with experience. These data provide a foundation for unpacking constructs like "social recognition" into multi-dimensional patterns, different components of which may be expressions of distinct motivation and learning processes.

Disclosures: A.L. Thatcher: None. **S. Cooke:** None. **K. Webb:** None. **K. Butler:** None. **N. Insel:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.10/R13

Topic: F.01. Neuroethology

Support: Packard Fellowship
McKnight Scholar Award
Alfred P. Sloan Research Fellowship
NYSCF-Robertson Investigator Award
NIH Director's New Innovator Award (DP2)
Klingenstein-Simons Fellowship Award in the Neurosciences
Pew Scholar Award

Title: A developmentally conserved neural signature of social-vocal communication in the motor cortex of Egyptian fruit bats

Authors: *M. C. ROSE, T. A. SCHMID, J. E. ELIE, M. M. YARTSEV;
Univ. of California Berkeley, Berkeley, CA

Abstract: Across species social communication often occurs through vocal interactions, yet the brain mechanisms that mediate social-vocal communication signals, especially under natural conditions, remain poorly understood. To better understand its neural basis, we chose to study social-vocal communication in the Egyptian fruit bat (*Rousettus aegyptiacus*). We chose this species for its mammalian brain organization, diverse social-vocal repertoire and vocal plasticity capabilities. We used lightweight, wireless electrophysiology to record neural activity from the Frontal Motor Area (FMA) of freely behaving bats and on-animal audio systems and microphones to precisely measure vocal production and perception during social interactions. Because previous reports have indicated that the Egyptian fruit bat's vocal repertoire undergoes developmental changes over the age range examined here, we looked for corresponding differences in neural activity. Next, as vocal production is exclusively tied to social behavior in Egyptian fruit bats, we looked for correlation in activity across brains during vocalization events. Finally, we asked how neural activity is affected by artificial laboratory training by comparing FMA activity during naturalistic social-vocal behavior to highly-trained vocal production behavior. Taking this approach, we assessed vocalization related FMA neural activity for: 1) differences between juveniles and adults 2) cross-brain neural synchrony and 3) differences between naturalistic and highly-trained vocal behavior. Combined, we present first steps toward understanding how motor cortical activity functions during social-vocal interactions.

Disclosures: **M.C. Rose:** None. **T.A. Schmid:** None. **J.E. Elie:** None. **M.M. Yartsev:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.11/R14

Topic: F.01. Neuroethology

Support: NIH DP2-DC016163
New York Stem Cell Foundation
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Klingenstein-Simons Fellowship

Title: Correlated neural activity across the brains of socially interacting bats

Authors: *W. ZHANG, M. M. YARTSEV;
Bioengineering, Univ. of California Berkeley, Berkeley, CA

Abstract: Social interactions occur between multiple individuals, but what is the detailed relationship between the neural dynamics across their brains? To address this question across timescales and levels of neural activity, we used wireless electrophysiology to simultaneously record from the frontal cortex of pairs of bats over ~100-minute-long sessions. During these sessions, the bats engaged in a wide range of natural social interactions, which we characterized at a detailed level. We found that neural activity was remarkably correlated between their brains over timescales from seconds to hours. The correlation depended on the two individuals sharing a social environment and was most prominent in high frequency local field potentials (>30 Hz) and local spiking activity, both of which are neural signals that were under-explored in similar previous studies in humans. Furthermore, the degree of neural correlation covaried with the extent of social interactions, and an increase in correlation preceded their initiation. Lastly, we characterized the neural representations of the social behaviors the interacting bats engaged in. Together, the results show that inter-brain neural correlation is an inherent feature of natural social interactions, reveal the domain of neural activity where it is most prominent, and provide a foundation for studying its functional role in social behaviors.

Disclosures: W. Zhang: None. **M.M. Yartsev:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.12/R15

Topic: F.01. Neuroethology

Title: Unraveling the evolution of brain networks for complex vocal behavior through comparative epigenomics across mammals

Authors: *M. WIRTHLIN[1], S. ANNALDASULA[1], I. KAPLOW[1], T. A. SCHMID[3], S. VERNES[5], W. R. STAUFFER[6], M. M. YARTSEV[4], A. R. PFENNING[2];
[2]Computat. Biol. Dept., [1]Carnegie Mellon Univ., Pittsburgh, PA; [3]Helen Wills Neurosci. Inst., [4]Bioengineering, Univ. of California Berkeley, Berkeley, CA; [5]Max Planck Inst. For Psycholinguistics, Nijmegen, Netherlands; [6]Neurobio., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Vocal behavior is a highly variable behavioral phenotype, ranging from simple grunts and hisses to the complex vocal learning exemplified by human speech. Although the neuroanatomical, electrophysiological, and molecular bases for this behavior are being explored in a handful of species, an overall picture of how genomic differences subserve this trait remain elusive. In the brain regions that control the production of learned vocalizations, we previously identified convergent changes in gene expression that were unique to multiple vocal learning species, and not present in their vocal non-learning relatives. Given the intriguing possibility suggested by these findings that there may exist fundamental genetic mechanisms for the evolution of this behavior, we sought to discover whether this convergence also exists at the level of the gene regulatory sequences that control gene expression. We assessed the epigenomic profile of several brain regions involved in vocal control in Rhesus macaque (Macaca mulatta) and the Egyptian fruit bat (Rousettus aegyptiacus) using ATAC-seq. Drawing from these and other publicly available open chromatin datasets, we developed and implemented an improved pipeline for mapping putative gene regulatory sequences across a wide range of mammalians species. Despite the extensive nucleotide sequence turnover occurring over the >150 million years of mammalian evolution, we were able to identify conserved sets of regulatory sequences displaying higher-than-expected overall conservation in brain-specific regulatory activity. We then analyzed the identified orthologous regulatory sequences to assess the possibility of sequence evolutionary rate convergence and differential transcription factor binding that could explain the differences in gene regulatory activity in brain regions specifically involved in vocal behavior, which could ultimately explain the evolution of phenotypic differences in vocal behavior observed across species. Our work points to genomic changes in gene regulatory sequences, rather than changes in genes themselves, as a hotbed for the evolution of mammalian vocal behavior. We discuss these findings within the framework of a novel hypothesis for the evolution of complex vocal behavior.

Disclosures: **M. Wirthlin:** None. **S. Annaldasula:** None. **I. Kaplow:** None. **T.A. Schmid:** None. **S. Vernes:** None. **W.R. Stauffer:** None. **M.M. Yartsev:** None. **A.R. Pfenning:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.13/R16

Topic: F.01. Neuroethology

Support: DFG Grant EXC 307

Title: Compensatory mechanisms affect sensorimotor integration during ongoing vocal-motor acts in marmoset monkeys

Authors: *J. LÖSCHNER, T. POMBERGER, S. R. HAGE;
CIN, Univ. of Tuebingen, Tuebingen, Germany

Abstract: In vertebrates, any transmission of vocal signals faces the challenge of acoustic interferences such as heavy rain, wind, animal, or urban sounds. Consequently, several mechanisms and strategies have evolved to optimize the signal-to-noise ratio. Examples to increase detectability are the Lombard effect, an involuntary rise in call amplitude in response to masking ambient noise, which is often associated with several other vocal changes such as call frequency and duration, as well as the animals' capability of limiting calling to periods where noise perturbation is absent. Previous studies revealed rapid vocal flexibility and various audio-vocal integration mechanisms in marmoset monkeys. Using acoustic perturbation triggered by vocal behavior, we show that marmosets are capable of rapidly modulating call amplitude and frequency in response to perturbing noise starting after call onset. The animals swiftly increased call frequency after noise onset indicating a rapid effect of perturbing noise on vocal motor pattern production. Call amplitudes were also affected. Interestingly, however, the marmosets did not exhibit the Lombard effect as previously reported but decreased their call intensity in response to perturbing noise. Our findings indicate that marmosets possess a general avoidance strategy to call in the presences of ambient noise and suggest that these animals are capable of counteracting a previously thought involuntary audio-vocal mechanism, the Lombard effect, presumably via cognitive control processes.

Disclosures: **J. Löschner:** None. **T. Pomberger:** None. **S.R. Hage:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.14/R17

Topic: F.01. Neuroethology

Support: DFG Grant EXC307
DFG Grant HA5400/3-1

Title: Single unit recordings in the brainstem of vocalizing marmoset monkeys

Authors: *T. POMBERGER, S. R. HAGE;
CIN, Univ. of Tuebingen, Tuebingen, Germany

Abstract: Chronic recordings with multi-electrode arrays are widely used to study neural networks underlying complex primate behaviors. Most of these systems are designed for studying neural activity in the cortical hemispheres resulting in a lack of devices being capable of simultaneously recording from ensembles of neurons in deep brainstem structures. However, to fully understand complex behavior, it is fundamental to also decipher the intrinsic mechanisms of the underlying motor pattern generating circuits in the brainstem. We report a light-weight system that simultaneously measures single-unit activity from a large number of recording sites in the brainstem of marmoset monkeys. It includes a base chamber fixed to the animal's skull and a removable upper chamber that can be semi-chronically mounted to the base chamber to flexibly position an embedded micro-drive containing a 32-channel laminar probe to record from various positions within the brainstem for several weeks. The current system is capable of simultaneously recording stable single-unit activity from a large number of recording sites in the brainstem of vocalizing marmoset monkeys. We found single unit activity that is correlated to vocal-motor output as well as auditory activity in deep brainstem structures. The semi-chronic implantation of laminar electrodes into the brainstem of behaving marmoset monkeys opens new research possibilities in fully understanding the neural mechanisms underlying vocal pattern generation in marmoset monkeys.

Disclosures: T. Pomberger: None. **S.R. Hage:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.15/R18

Topic: F.01. Neuroethology

Support: DFG Grant EXC 307

Title: Arousal states underlying vocal behavior in macaque monkeys

Authors: *C. RISUENO SEGOVIA[1], P. CHAMPEROUX[2], S. R. HAGE[3];
[1]Werner Reichardt Ctr. For Integrative Neuroscien, Tübingen, Germany; [2]Ctr. de Recherches Biologiques, Baugy, France; [3]CIN, Univ. of Tuebingen, Tuebingen, Germany

Abstract: Long-tailed macaques (*Macaca fascicularis*) have an extensive vocal communication repertoire, which they use in a variety of behavioral contexts. However, the physiological states underlying this behavior are still largely unknown. According to recent publications, arousal dynamics are linked to vocal output in marmoset monkeys. In this study, we investigate the correlation of vocal behavior in freely moving cynomolgus monkeys with several measures of the autonomic nervous system. For that, we use wireless transmitters implanted in the monkeys to telemetrically monitor ECG, blood pressure and activity, and relate these measures with simultaneously recorded vocalizations. Our results indicate that the vocal production of cynomolgus monkeys is coupled with different parameters of the autonomic nervous system such as heart rate, respiratory rate, ECG waveform and blood pressure.

Disclosures: C. Risueno Segovia: None. **P. Champeroux:** None. **S.R. Hage:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.16/R19

Topic: F.01. Neuroethology

Support: NIH Grant GM120782

Title: Genomic responses to selection for behavior in tame and aggressive foxes

Authors: *A. V. KUKEKOVA[1], J. L. JOHNSON[1], H. M. RANDO[1], L. N. TRUT[2];
[1]Animal Sci., Univ. of Illinois at Urbana-Champaign, Urbana, IL; [2]Inst. of Cytology and Genet. of the Russian Acad. of Sci., Novosibirsk, Russian Federation

Abstract: Tame and aggressive strains of red fox (*Vulpes vulpes*) have been developed in the famous long-term selective breeding program known as the Russian farm-fox experiment. We sequenced and assembled the red fox genome and re-sequenced a subset of foxes from the tame, aggressive, and conventional farm-bred populations to identify genomic regions associated with the response to selection for behavior. Analysis of the resequenced genomes identified 103 regions with either significantly decreased heterozygosity in one of the three populations or increased divergence between the populations. A strong positional candidate gene for tame behavior was highlighted: *SorCS1,* which encodes the main trafficking protein for AMPA glutamate receptors and neurexins and suggests a role for synaptic plasticity in fox domestication. Other regions identified as likely to have been under selection in foxes during domestication include genes implicated in human neurological disorders, mouse behavior, and dog domestication. The fox represents a powerful model for the genetic analysis of affiliative and aggressive behaviors that can benefit genetic studies of behavior in dogs and other mammals, including humans.

Disclosures: A.V. Kukekova: None. **J.L. Johnson:** None. **H.M. Rando:** None. **L.N. Trut:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.17/R20

Topic: F.01. Neuroethology

Title: The effects of simulated predation on shoaling behavior in zebra fish (Danio rerio)

Authors: *J. BOLES, I. TILMONT, J. MONELLY, E. YORK, K. POND, O. TUMINELLI, A. JOHNSON, K. WIENS, A. VELKEY;
Christopher Newport Univ., Newport News, VA

Abstract: Zebrafish (Danio rerio) are emerging as a useful model to investigate cognitive and behavioral disorders, including anxiety and post-traumatic stress disorder. Individual zebrafish responses to anxiogenic stimuli have been well documented, but anxiety behaviors within a social context are less understood. Zebrafish innately form shoals with one another, and aggregated zebrafish exhibit unique behaviors, which makes shoaling a powerful tool in investigating how social interaction influences individual zebrafish behaviors. The current study seeks to understand the effects of a social context on fear responses in zebrafish. Using a novel

three-chamber stimulus avoidance paradigm, shoals of six zebrafish were exposed to models of a sympatric predator, a freshwater needle-nose gar (Xenentodon cancila), of varying fidelity. These models included a live needle-nose gar, a video recording of the needle-nose gar, and a realistic motorized lure. Behaviors were analyzed with an automated behavior tracking software for average distance between fish, time spent in each zone of the tank, number of transitions between zones, average swim speed, swim speed variability, and time spent freezing. Against all stimuli, shoals spent more time at the bottom of the observation tank, confirming the anxiogenic nature of these models, but the live predator elicited the most robust diving response. In addition, the live predator evoked the most distinct avoidance response, while the video yielded mixed zone preferences, and the motorized model appeared to induce an approach response. These findings suggest that zebrafish are able to distinguish between similar visual stimuli, such as a live predator and recorded predator, and shoaling may reduce the potency of these stimuli, making a more realistic stimulus necessary in research. This project serves as a basis from which experimenters can further dissect the anxiety responses in aggregated zebrafish, enhancing neuroscientists' understanding of the zebrafish behavioral model with respect to psychiatric disorders and social behavior.

Disclosures: **J. Boles:** None. **I. Tilmont:** None. **J. Monelly:** None. **E. York:** None. **K. Pond:** None. **O. Tuminelli:** None. **A. Johnson:** None. **K. Wiens:** None. **A. Velkey:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.18/S1

Topic: F.01. Neuroethology

Title: Sexually dimorphic behavioral responses in zebrafish social choice

Authors: T. BETTS[1], I. DANSTROM[1], J. BOLES[1], L. O'NEIL[1], E. YORK[1], K. POND[1], G. SCHOLERFIELD[1], J. PARKER[1], M. CIRA ANGEL[1], K. ELEFTERIOU[1], R. TALIBI[1], A. J. VELKEY[1], ***K. M. WIENS**[1,2];
[1]Christopher Newport Univ., Newport News, VA; [2]Bay Path Univ., Longmeadow, MA

Abstract: Zebrafish (*Danio rerio*) are an excellent model organism for the comparative study of vertebrate social behavior. One characteristic of zebrafish social behavior is their tendency to aggregate in groups, known as shoals. Zebrafish exhibit sexually dimorphic behavior in swimming patterns, shoal size preference, aggression, and habitat. However, it is unknown if zebrafish exhibit sex differences when subjects are given a choice between social stimuli of varying visual fidelity. This study examined the behavioral responses of male and female zebrafish after the presentation of three variations of social stimuli: live shoal, video-recorded shoal, and a motorized lure mimic. Responses were analyzed with Ethovision XT 10 to identify

behavioral response patterns related to location within the tank, swim velocity, moving versus freezing, or zone transitions. Consistent with our previous studies, both sexes displayed a preference for live conspecifics over motorized or video shoals. However, this new study indicated that males and females had distinct responses to the different stimuli. Males were more exploratory in all stimuli combinations, and tended to prefer the bottom corners of the tank. In contrast, female zebrafish generally used the entire column to inspect the preferred stimuli and were less exploratory across stimuli. Our findings suggest that this aspect of zebrafish social behavior is sexually dimorphic.

Disclosures: **T. Betts:** None. **I. Danstrom:** None. **J. Boles:** None. **L. O'Neil:** None. **E. York:** None. **K. Pond:** None. **G. Scholerfield:** None. **J. Parker:** None. **M. Cira Angel:** None. **K. Elefteriou:** None. **R. Talibi:** None. **A.J. Velkey:** None. **K.M. Wiens:** None.

Poster

498. Vocalization and Social Behavior in Non-Avian Species

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 498.19/S2

Topic: F.01. Neuroethology

Title: Early social isolation reduces social interactions in adult planarians and reduces neural activation in sensory processing brain regions

Authors: *S. GUARIGLIA[1], S. M. ORTIZ[2], B. KOLSIN[2], C. KNAPSKI[2];
[1]New York State Inst. for Basic Res., Staten Island, NY; [2]St. Josephs by the Sea HS, Staten Island, NY

Abstract: Planarians are routinely used to study regeneration and early development. Following head amputation, planarians are capable of regenerating their brain within seven days. In an attempt to characterize planarians for their utility in studying neurodevelopment, our laboratory is interested in identifying and characterizing behaviors that are relevant to disorders of neurodevelopment, namely Autism Spectrum Disorders (ASD). Therefore, the objective of this work was to determine if planarians engage in social interactions and if so, to identify the anatomical regions in the planarian brain that are involved in the regulation of social behavior. To assess planarian social interactions, we developed and validated a novel behavioral assay that allows for rapid and reproducible identification of social interactions. In the assay, planarians are placed into a novel open field, and their spatial location is recorded every ten minutes. The nearest neighboring distance (NND) between planarians is averaged at each time point. We were able to demonstrate that exposure to MK-801, a potent NMDA receptor antagonist which is known to impair social interactions in other model organisms, increased the NND between planarians, suggesting that social interactions in planarians are also reduced. Once our assay was validated, we went on to determine if the environment of planarian development could influence

adult social behavior. In our first set of these experiments, we demonstrated that planarians who develop in isolation (individually housed planarians; IHP) are less social than planarians that are left to develop in a group setting (Group-Housed Planarians; GHP; $p < 0.0001$; $F(7,144) = 161.1$). We then went on to map the brain regions that are involved in the regulation of social behavior using c-fos expression as an indicator for neural activity. We were able to determine that GHP have a significant increase in neural activation as compared to IHP when presented with diffusible social cues from novel planarians ($p < 0.0001$; $F(3,8) = 215.8$). Finally, we were able to demonstrate that c-Fos expression patterns change and are most prevalent in the signal processing regions in cephalic branches IV-IX when they are presented with social cues. Together, our work introduces a novel, high throughput behavioral assay for the assessment of social interactions in planarians along with functional anatomical correlates of the planarian brain which regulate such social interactions. Since planarians share many primary neural correlates with vertebrate systems, our work may be useful for teasing out intricacies in the understanding of social behavior.

Disclosures: **S. Guariglia:** None. **S.M. Ortiz:** None. **B. Kolsin:** None. **C. Knapski:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.01/S3

Topic: F.02. Behavioral Neuroendocrinology

Support: NIA Grant R21AG048463

Title: Resting state functional connectivity under stress differs across the hormonal contraceptive cycle

Authors: *A. Y. HERRERA[1], P. NASSERI[2], K. GILLETTE[3], S. FAUDE[3], J. WHITE[3], R. VELASCO[3], M. MATHER[1];
[1]Leonard Davis Sch. of Gerontology, [2]Neurosci. Grad. Program, [3]USC, Los Angeles, CA

Abstract: Previous studies indicate a negative correlation between stress-induced change in cortisol and functional connectivity of memory circuits, including between right and left hippocampus and between parahippocampus and left middle temporal gyrus. However, this work is limited to men. Women using hormonal contraceptives (HC) are reported to show similar memory patterns to men, however, they also show smaller cortisol responses to stress than men. In this study, we aimed to investigate the relationship between cortisol response to stress and resting state functional connectivity (rsFC) after stress in women using hormonal contraceptives. We used pulsed arterial spin labeling (PASL) to investigate rsFC of memory circuit regions after stress in women using 28-day monophasic HC. To examine the effects of synthetic hormones,

we tested twenty healthy young women twice across the HC cycle, once during days 8 to 21 (hormone-present phase) and once during days 24 to 28 (hormone-absent phase). In each phase, women completed the cold pressor test to increase cortisol levels and completed a resting state scan 40 minutes after stress onset. Right and left hippocampus, bilateral parahippocampus and left middle temporal gyrus were selected as seed regions for rsFC analyses. Based on the associations between change in cortisol and rsFC summarized above, we specifically tested the association between change in cortisol from baseline to 40 minutes after stress onset and rsFC between: 1) left and right hippocampus and 2) bilateral parahippocampus and left middle temporal gyrus.We found that change in cortisol was significantly negatively correlated with rsFC between bilateral parahippocampus and left middle temporal gyrus during the hormone-present phase. We found no relationship between change in cortisol and rsFC between left and right hippocampus during this phase. No associations were found for hormone-absent phase.Our results suggest that stress exerts different effects on rsFC of memory circuit regions across the contraceptive cycle. Based on other work showing better verbal memory during the hormone-present phase and the role of left middle temporal gyrus in verbal learning and memory recall, our findings suggest women may be offered some protection against stress effects on verbal memory during the hormone-present phase. Further studies are needed to investigate the factors modulating this association across the contraceptive cycle.

Disclosures: A.Y. Herrera: None. **P. Nasseri:** None. **K. Gillette:** None. **S. Faude:** None. **J. White:** None. **R. Velasco:** None. **M. Mather:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.02/S4

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 1R01HD093907-01A1

Title: Alterations in progesterone activity affects serotonergic innervation of the medial prefrontal cortex and produces deficits in complex cognitive behaviors

Authors: *A. PHILLIPS[1], C. K. WAGNER[2];
[1]Univ. at Albany State Univ. of New York, Albany, NY; [2]Univ. Albany, Albany, NY

Abstract: The mesocortical serotonergic pathway, comprised of innervation of the medial prefrontal cortex (mPFC) arising from serotonergic neurons in the dorsal raphe nuclei (DRN) of the midbrain, regulates complex cognitive function in adulthood. Disruptions in the normal development of this pathway may produce deficits in complex cognitive behaviors in adulthood. Progesterone receptor (PR), a powerful transcription factor, is transiently expressed within the

DRN and layers II/III of the mPFC during periods of synaptogenesis in this circuit, suggesting that PR activity during postnatal life may play a critical role in the maturation of the mesocortical serotonergic pathway. In the present studies, pharmacological inhibition of PR activity or exposure to the synthetic progestin, 17α-hydroxyprogesterone caproate (17-OHPC), neonatally decreased the density of SERT-ir fibers in the prelimbic mPFC at P28 in layers I, V and VI. Further, decision making, as measured in the delay discounting task, was altered and anxiety-like behavior was increased in the elevated plus maze in adulthood following neonatal administration of 17-OHPC. These findings have clinical implications as 17-OHPC is administered to pregnant women at-risk for premature birth.

Disclosures: A. Phillips: None. **C.K. Wagner:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.03/S5

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 1R01HD093907-01A1

Title: Clinically relevant synthetic progestin alters medial prefrontal cortex microglial phenotype and density in a sex-specific manner

Authors: *M. LOLIER, C. K. WAGNER;
Univ. at Albany, Albany, NY

Abstract: 17-alpha-hydroxyprogesterone caproate (17-OHPC) is a synthetic progestin commonly prescribed to pregnant women at risk for recurrent preterm birth. 17-OHPC can be transferred from the maternal compartment to the fetal compartment of the placenta *in situ*, and is detected in the fetal plasma up to 44 days after the last injection. The potential impact on cortical development should not be overlooked, as the timing of 17-OHPC administration coincides with critical periods of mesocortical dopamine pathway development, a neural circuit that regulates complex cognitive behaviors. In rodent models, nuclear progesterone receptor (PR) is expressed in dopaminergic neurons in the ventral tegmental area (VTA) that project to the medial prefrontal cortex (mPFC). 17-OHPC administration during development results in significant changes in dopaminergic innervation of layer 5 of the prelimbic area (PL) of the mPFC in a sex specific manner. 17-OHPC treated females have a significantly narrower tyrosine hydroxylase-ir (THir) fiber dispersion than control females, with no treatment differences in males. The significant decrease in THir dispersion in 17-OHPC treated females abolishes a sex difference observed in control animals. These changes in early innervation are believed to contribute to the deficits in cognitive flexibility observed in adulthood. In the present study, the

effects of 17-OHPC on microglia were examined. Preliminary results demonstrate a sex difference in microglia morphology in which control females have more microglia with an activated phenotype than males. This sex difference is abolished with 17-OHPC treatment such that 17-OHPC treated females have significantly fewer microglia with an activated phenotype than control females, and have comparable numbers to 17-OHPC males. Additionally, there is a trend toward significant differences in the density of microglia, in which 17-OHPC females have fewer microglia than control females, and 17-OHPC males have more microglia than control males. Results suggest that exposure to 17-OHPC during development may fundamentally alter cortical development perhaps, in part, through changes in microglia function. Consideration should be given to the potential effects of 17-OHPC on neural development in children.

Disclosures: M. Lolier: None. **C.K. Wagner:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.04/S6

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant 1R15AG042155

Title: Dose-dependent effects of testosterone on spatial learning strategies and brain-derived neurotrophic factor in male rats

Authors: *M. D. SPRITZER[1], K. J. ZHANG[1], R. A. RAMDEV[2], N. J. TUTA[2];
[1]Biol., [2]Neurosci., Middlebury Col., Middlebury, VT

Abstract: We have previously shown that testosterone has complex dose-dependent effects on spatial working memory in male rats. Additionally, a low physiological dose of testosterone biased males toward using a response strategy, whereas a high physiological dose biased males toward using a place strategy. The primary goal of this experiment was to determine whether the demonstrated preference for a particular learning strategy was associated with a better ability to employ that strategy on a spatial task. Additionally, we tested whether brain-derived neurotrophic factor (BDNF) might be a mechanistic link between testosterone and spatial memory. All rats (n = 10-15/group) were bilaterally castrated and given one of three daily injection doses of testosterone propionate (0.125, 0.250, or 0.500 mg/rat) or the drug vehicle (control group) starting 7 days prior to the first day of behavioral testing. A plus-maze was used to test rats on either a place task (learning the position of a goal arm relative to distal spatial cues) or a response task (learning to turn a particular direction). All rats were given 100 trials on the maze, and criterion was reached when a rat made 9 out of 10 correct choices. We found that a lower testosterone dose (0.125 mg) significantly improved rats' performance on a response task,

whereas a higher testosterone dose (0.500 mg) improved a rats' performance on a place task. Rats injected with an intermediate dose (0.250 mg) performed poorly on both tasks, presumably because these rats were unable to effectively employ either spatial strategy effectively. Brain tissue from the prefrontal cortex, hippocampus, and striatum was collected 24 h following behavioral testing, and ELISAs were used to quantify concentrations of brain-derived neurotrophic factor (pro- and mature-BDNF). Testosterone had significant dose-dependent effects on BDNF levels in the hippocampus and striatum, but not the prefrontal cortex. Though there were some differences between the place and response experiments, a low dose of testosterone (0.125 mg) increased total BDNF in the striatum, and a high dose (0.500 mg) increased total BDNF in the hippocampus. Mature BDNF and proBDNF levels correlated with each other. Learning the place-task relies on hippocampal function, whereas learning the response-task relies on striatal function. Thus, the same doses of testosterone that enhanced learning on the place and response tasks, enhanced BDNF levels in the expected brain regions, hippocampus and striatum, respectively.

Disclosures: **M.D. Spritzer:** None. **K.J. Zhang:** None. **R.A. Ramdev:** None. **N.J. Tuta:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.05/S7

Topic: F.02. Behavioral Neuroendocrinology

Support: Research funded by the Cancer Prevention & Research Institute of Texas RP180055
NIH NCI research grant R01 CA224672

Title: Cognitive impairments induced in a middle aged rodent model of androgen deprivation therapy for prostate cancer are reversed with the antidepressant vortioxetine

Authors: *A. M. SHARP[1,2], A. DORNBUSCH[3,4], J. GELFOND[5], T. L. JOHNSON-PAIS[3,4], R. J. LEACH[6,4,7], M. LISS[6,4,10], A. C. SULLIVAN[2,8,9], I. M. THOMPSON[6,11], D. MORILAK[1,2,4,10]; [1]Dept. of Pharmacol., [2]Ctr. for Biomed. Neurosci., [3]Cell Systems & Anat., [4]Mays Cancer Ctr., [5]Dept. of Epidemiology & Biostatistics, [6]Dept. of Urology, [7]Dept. of Cell Systems & Anat., [8]Dept. of Neurol., [9]Glenn Biggs Inst. for Alzheimer's & Neurodegerative Dis., UT Hlth. San Antonio, San Antonio, TX; [10]South Texas Veterans Hlth. Care Service, San Antonio, TX; [11]Dept. of Urology, CHRISTUS Santa Rosa Hosp., San Antonio, TX

Abstract: Androgen deprivation therapy (ADT) is the primary treatment for late-stage prostate cancer. However, it is associated with several serious side effects, including profound cognitive impairment that is observed in more than half of patients treated with ADT. This significantly

reduces quality of life for cancer survivors and their families. It is important to improve the cognitive side effects of ADT, as approximately 44.8% of patients will undergo this type of treatment. The most prominent deficits observed in patients are observed in cognitive domains mediated by the medial prefrontal cortex (mPFC) and hippocampus (Hipp), including executive function and spatial recognition memory, respectively. Thus, to address the mechanisms underlying these effects, we have used the Attentional Set-shifting Test (AST) and the Novel Object Location (NOL) Test to assess cognitive function after surgical castration as a rodent model of ADT. Preliminary studies in our lab indicate that ADT-induced cognitive impairments on these tasks in young-adult Sprague Dawley rats can be reversed with chronic administration of a novel multimodal antidepressant, vortioxetine (VTX; 28 mg/kg/day for 2 weeks). This suggests that VTX, which has proven efficacy in improving cognitive impairment associated with depression, may be a novel therapeutic to alleviate ADT-induced cognitive impairments as well. Because prostate cancer primarily afflicts men around the age of 65, cognitive impairments in ADT-patients may be influenced by age-related cognitive decline. Therefore, to investigate the potential interaction of age and ADT, we are investigating effects in middle-aged 12-month-old rats, an age at which mild age-related cognitive impairments begin to emerge. We hypothesize that castration will induce cognitive impairment in middle-aged rats as it did in young adult male rats, and the deficits may be exacerbated in the aged rats. Further, we hypothesize that VTX will reverse the deficits in castrated middle-aged animals, as it did in the younger population. Early results indicate that VTX is able to reverse deficits associated with ADT in middle-aged animals on the AST and NOL tests back to levels comparable to intact aged controls. These studies are ongoing. Experiments are underway to investigate changes in functional connectivity of the mPFC and dHipp in the aged population by measuring changes in evoked local field potentials. Overall, this project may identify new targets for reversing cognitive impairment after ADT for the treatment of prostate cancer.

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Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.06/S8

Topic: F.02. Behavioral Neuroendocrinology

Support: NSERC Grant

Title: Mental rotation task performance in a gender diverse Thai sample: A test of neurohormonal theory

Authors: *L. T. THURSTON[1], M. N. SKORSKA[2], D. E. PERAGINE[1], L. A. COOME[1], D. P. VANDERLAAN[2];
[1]Psychology, Univ. of Toronto, Toronto, ON, Canada; [2]Psychology, Univ. of Toronto Mississauga, Mississauga, ON, Canada

Abstract: Sex differences in visuospatial cognition have been reported in cisgender individuals with an advantage for cismen; mental rotation task (MRT) performance shows this robust difference. MRT performance also varies by circulating hormone concentrations, with low-estrogen phases of the menstrual cycle associated with higher performance in naturally cycling ciswomen. The literature has yet to corroborate performance differences across gender identity (GI) *and* sexual orientation (SO), both of which could undermine the expected sex difference due to the neurohormonal hypothesis that GI and SO are influenced by the direction of masculinization or feminization of neurodevelopment. Organizational effects suggest that prenatal exposure to androgens alters the masculinization of the developing brain. Activational effects postulate that circulating androgens and estrogens, coupled with this prenatal organization, augment either more culturally masculine or feminine behaviour, respectively. To test whether sex differences in cognition are influenced by GI and SO, MRT performance was assessed in a gender diverse sample of Thai participants (*N=981*) and evaluated by hormone profile. To explore organizational effects, individuals were categorized by self-reported GI and SO. Where applicable, the recency and consistency of feminizing hormone therapy (HT) or menstrual cycle were considered on the pretense that the duration and regularity of estrogens negatively influence MRT score.
Our sample replicated the male advantage; straight cismen outperformed all groups. Gay cismen outperformed straight ciswomen but did not differ from *sao praphet song*, feminine third gender individuals assigned male at birth, who performed comparably to the assigned female at birth groups. These results could reflect prenatal feminization. Further, *sao praphet song* using HT had marginally lower scores than those not currently on HT, but the consistency and age of first HT use were not related to MRT score. In straight ciswomen, those in the follicular phase had similar performance to straight cismen, but those in higher estrogen phases had significantly lower scores. Overall, GI, SO, and current hormone profile were related to performance, suggesting that both organizational and activational effects impact the expected psychological sex differences. By examining visuospatial cognition in a non-Western, gender diverse sample, these data enhance our understanding of sex differences in cognition and emphasize the importance of recognizing GI and SO in future studies of visuospatial cognition.

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Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.07/S9

Topic: F.02. Behavioral Neuroendocrinology

Support: NIMH K01MH109712

Title: Examination of sex differences in the dorsal raphe serotonin

Authors: H. O. CAIOLA, *B. D. ROOD;
Cell Biol. and Neurosci., Rowan Univ. Sch. of Osteo. Med., Stratford, NJ

Abstract: Dysregulation of the serotonin (5-HT) system is common among a number of mental disorders that affect mood and social behavior; incidence and severity of disorders impacted by 5-HT dysregulation are often different between men and women. For example, women have a higher incidence of anxiety and depression, whereas autism and schizophrenia are more common in men. Cells that provide 5-HT throughout the forebrain are found in the dorsal raphe nucleus (DR). Because many 5-HT neurons express gonadal steroid receptors, it is possible that different levels of circulating gonadal steroid hormones or differential expression of receptors in 5-HT neurons could result in sex differences in mood and behavior. Notably, the sex hormone estradiol regulates 5-HT-related genes including those involved in 5-HT synthesis (tryptophan hydroxylase, TPH), 5-HT reuptake (5-HT transporter), and the 5-HT 1A receptor. In rats, males have higher basal firing rates of DR 5-HT neurons than females. Based on the presence of gonadal steroid receptors and evidence for sex differences in neuron function, we hypothesize that gonadal steroid hormones impact 5-HT cell physiology in mice, which could lead to sex differences in function. To test this hypothesis, we examined the co-localization of estrogen receptor alpha (ERα) and TPH throughout the DR of male and female mouse brains. We did not find any sex differences in the proportion of 5-HT (TPH+) cells containing ERα, but we did observe regional variation. In the lateral wings, approximately 20% of 5-HT neurons expressed ERα, whereas 25-45% of 5-HT neurons in the dorsomedial (DMDR) and ventromedial nuclei (VMDR) expressed ERα. In the VMDR and DMDR there was also a rostral to caudal gradient with a higher proportion of caudal TPH+ neurons co-localizing with ERα (ANOVA; VMDR: $F_{(3,39)}=6.955$, $p=0.0007$ and DMDR: $F_{(3, 39)}=5.716$, $p=0.002$). Using whole cell patch clamp techniques, we examined membrane characteristics (tau, resistance, resting membrane potential), action potential properties (threshold, duration, amplitude), and firing rates (spike induced by current injection from 0 to 180 in +20 pA steps) of 5-HT neurons in male (n=23 cells) and female (n=23 cells) mice. We did not observe sex differences in any of the measures listed above; however, we do not know whether or not recorded neurons contained estrogen receptors. Ongoing work seeks to determine whether gene expression differs between male and female

serotonin neurons and whether patterns of gene expression depend on the presence of gonadal steroid receptors. We are also examining whether the presence of ERα influences electrophysiological measures.

Disclosures: H.O. Caiola: None. **B.D. Rood:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.08/S10

Topic: F.02. Behavioral Neuroendocrinology

Title: Melatonin and 5-methoxytryptophol effects on locomotor activity, glycemic index, and weight of testes and seminal vesicles of young rats

Authors: *A. VAZQUEZ-ALVAREZ[1], F. ZAPATA DENOVA[2], B. PRIETO-GOMEZ[3], C. REYES-VAZQUEZ[4];
[1]Physiol., Univ. Nacional Autónoma de México, Mexico, D.F., Mexico; [2]Physiol., UNAM, Mexico, D.F., Mexico; [3]Univ. Nacional Autonoma Mexico, 04510 DF, Mexico; [4]Dept. De Fisiología, Mexico, D.F., Mexico

Abstract: Melatonin and 5-metoxyitryptophol, the main indol hormones secreted by the pineal gland, are considered modulators of various physiological activities. Many of their actions are only observed with pharmacological doses. In this project, these indols was administered to 54 male Wistar rats of 4 weeks old, weighing 120 to 140g. Two rats were placed in each acrylic box with woodchips bed, dark-light cycles 12:12, temperature of 22-24 °C and free access to water and food. The experiment was carried out following the norm NOM-062-ZOO-1999. Rats were divided into three groups, a control group that received vehicle 0.1 ml / kg / day, intraperitoneally (i.p.) for 1,2 or three weeks; group 2 received 5-methoxytryptophol i.p. 15mg / kg / day, for 1, 2 or 3 weeks, and group 3 received Melatonin i.p. 15mg / kg / day for 1, 2 or 3 weeks. At the end of the corresponding administration time, rats were individually subjected to spontaneous locomotor activity measurement, for 60 min at same time each day. In addition, glucose concentration was recorded. At the end of these experiments, rats were sacrificed with an overdose of sodium pentobarbital and the testicles and seminal vesicles were removed and weighted. Differential effects were observed between melatonin and 5-methoxytryptophol. Rats treated for 3 weeks after weaning with melatonin showed a locomotor activity, significantly higher than those treated with 5-methoxytryptofol or vehicle. The weight of the testes and the seminal vesicles was lower after the first week of administration with melatonin and from the second week with 5-methoxytryptophol. There were no significant differences between the groups in terms of blood glucose concentration. These results showed that both indoles had

effects on the spontaneous locomotor activity and the development of their sexual organs. However, the effects had different timing and intensity.

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Poster

499. Hormone Modulation of Behavior and Physiology II

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Program #/Poster #: 499.09/S11

Topic: F.02. Behavioral Neuroendocrinology

Support: SC2 GM122646-03
NSF GRFP 201825283

Title: Estrogen fluctuations modulate electrophysiological properties of ventral tegmental area dopamine neurons to alter event salience

Authors: *M. SHANLEY[1], Y. MIURA[1], R. KAMALETDINOVA[2], R. KARIM[2], E. BLICKER[2], A. K. FRIEDMAN[2];
[1]The Grad. Center, City Univ. of New York, New York, NY; [2]Hunter College, City Univ. of New York, New York, NY

Abstract: The ventral tegmental area (VTA) is a dopaminergic nucleus involved in regulating the behavioral response to reward and aversion. Dysregulation of VTA dopamine neurons has been associated with a wide array of neuropsychiatric conditions such as depression, anxiety, and addiction. Many of these disorders exhibit a sex difference and show cyclic changes in severity that coincide with hormonal fluctuations across the menstrual cycle. Despite these observations, the role of hormones in regulating the electrophysiological activity of VTA dopamine neurons remains understudied. Of the various hormones involved in the reproductive cycle, estrogens have been shown to alter the activity of neurons in several different brain regions through modulation of potassium (K+) channels via changes in transcription of channel subunits and post-translational modifications. Further, a population of VTA dopamine neurons expresses estrogen receptors. We hypothesize that estrogen signaling modulates the level of activity of K+ channels in the VTA, and this modulation primes dopamine neurons to respond differently to salient stimuli depending on local levels of estrogen. We utilize a mouse model (C57Bl/6J) to examine the how estrogen modulates experience-dependent plasticity of dopamine neurons. Female mice undergo a 4-5 day estrous cycle, in which serum estrogen levels decline rapidly during estrus. Using whole cell slice electrophysiology, we characterized the physiological response of VTA dopamine neurons to estrogen signaling and withdrawal. We found that both serum levels of 17β-estradiol, measured through ELISA, and *in vitro* bath application of 17β-

estradiol modulate the activity of A-type and M-type K+ currents. During estrogen withdrawal there is a significant reduction in K+ currents, which leads to an increase in neuronal excitability. To determine if the changes in neuronal activity, due to estrogen signaling, alter behavioral responses to a salient experience, we utilized a one-day acute stress model and pharmacologically manipulated local estrogen concentrations through a chronic cannula implant. We then examined the behavioral phenotype the following day. Infusing the estrogen receptor antagonist ICI 182,780 into the VTA of male and female mice during stress acquisition leads to reduction in social behaviors. We also demonstrate that disruption of local estrogen synthesis with an aromatase inhibitor during stress acquisition leads to a reduction in social behaviors. Together, our results indicate that the role of estrogen fluctuations in the VTA is a critical modulator determining the behavioral impact of stress.

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Poster

499. Hormone Modulation of Behavior and Physiology II

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Program #/Poster #: 499.10/S12

Topic: F.02. Behavioral Neuroendocrinology

Support: University at Buffalo Research Foundation, Award #64755
National Science Foundation , IOS-1754878

Title: Prepubertal ovarian inhibition of exploration and novelty seeking in Siberian hamsters: Does estradiol play a role?

Authors: *A. BARRETT, R. F. KYNE, L. M. BROWN, M. J. PAUL;
Psychology, Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: The overwhelming majority of research on the role of gonadal hormones in behavioral development has focused on perinatal, pubertal, or adult life stages. The juvenile period has been overlooked because it is thought to be a time of gonadal quiescence. In the present study, we tested whether prepubertal gonadectomy at postnatal day (P)15 impacts the behavior of male and female juvenile hamsters on the Light/Dark Box, Novel Object, and Social Approach tests at P30 (Experiment 1) and compared these findings to those obtained after adult gonadectomy, (surgery conducted at ~P80 and behavior testing at ~P106; Experiment 2). Prepubertal ovariectomy increased exploration (i.e. time spent in the light zone of the Light/Dark Box) and novel object investigation of juveniles indicating an inhibitory role for the juvenile ovary; social approach was unaffected. In contrast, adult ovariectomy and castration (both prepubertal and adult) had no effect on any behavioral measure. These findings suggest that ovarian inhibition of exploration

and novelty seeking is restricted to the juvenile phase. Experiment 3 tested whether rearing hamsters in a short day length (SD), which delays puberty in this species, extends the interval of juvenile ovarian inhibition on exploration and novelty seeking. We also tested whether provision of estradiol reverses the effects of prepubertal ovariectomy. SD-reared hamsters were gonadectomized or sham-operated and provided with blank, cholesterol, or estradiol capsules at ~P80 and underwent behavioral testing at ~P106; ages at which long day-reared hamsters are adult (as in Experiment 2), but SD-reared hamsters remain reproductively immature. Ovariectomy again increased exploration in the SD-reared juveniles despite the older age of surgery and testing. Estradiol treatment had no effect. These findings reveal a novel inhibitory role for the juvenile ovary in exploration and novelty seeking and suggest that estradiol on its own is not sufficient to mediate these inhibitory actions. Ongoing experiments administering letrozole to long day-reared juvenile Siberian hamsters are testing whether estradiol is necessary for juvenile ovarian inhibition of Light/Dark Box exploration.

Disclosures: A. Barrett: None. **R.F. Kyne:** None. **L.M. Brown:** None. **M.J. Paul:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

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Program #/Poster #: 499.11/S13

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH/NIDA R01DA034022
Howard Hughes Medical Institute Gilliam Fellowship
NIH D-SPAN F99 NS108515

Title: A specialized serotonergic neuron subtype responsive to dopamine and central to behavior

Authors: *K. LYON, S. M. DYMECKI;
Harvard Med. Sch., Boston, MA

Abstract: Serotonergic (5-HT) neurons modulate diverse behavioral and physiological functions. Increasingly, 5-HT neurons are described as a heterogeneous group comprised of distinct subpopulations specialized to regulate distinct biological processes and functions. One such subpopulation that modulates social behavior in mice is distinguished by expression of the type-II dopamine receptor (*Drd2*) and the pan serotonergic transcription factor Pet1. We refer to these as *Drd2- Pet1* 5-HT neurons. *In vivo* silencing of *Drd2-Pet1* 5-HT neurons drives heightened aggression and increased exploratory activity. While brain slice electrophysiology demonstrates that their excitability is inhibited cell-autonomously via DRD2 signaling, the requirement for DRD2 receptor activity in these serotonergic neurons for specific behavioral outcomes is unknown. To query the functional requirement for DRD2 in *Drd2-Pet1* 5-HT

neurons, we generated mice with serotonin specific deletion of the *Drd2* gene (*Drd2*-CKO) and administered a panel of behavioral assays. We find that *Drd2*-CKO males exhibit altered social dominance behavior. Further, *Drd2*-CKO females display altered acoustic responses compared to control littermates. These findings suggest an additional role for *Drd2-Pet1* 5-HT neurons in the modulation of auditory processing and/or sensorimotor gating. Interestingly, *Drd2-Pet1* 5-HT neurons have axonal projections to many brain regions involved in auditory processing. Using intersectional genetic tools to map the projections of *Drd2-Pet1* 5-HT neurons in both males and females, we seek to uncover sex-specific circuitry of this serotonergic neuron subtype that may underlie differential auditory processing as well as projections to brain regions involved in other sensory modalities.

Disclosures: K. Lyon: None. **S.M. Dymecki:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.12/S14

Topic: F.02. Behavioral Neuroendocrinology

Support: Kakenhi Grant 17K08512

Title: Increased social interaction and anxiety-like behaviors in FLRT2 deficient mice

Authors: *S. YAMAGISHI[1], F. ETO[2], Y. SHINODA[3], S. OGAWA[4], I. YAO[2,5], K. TAKAO[6,7], T. MIYAKAWA[8,7], K. SATO[1];
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Abstract: During cortical development, migrating neurons and pathfinding axons are guided by molecular cues within the extracellular matrix or on the surface of ambient cells. These cues are interpreted as attractive or repulsive, depending on the set of receptors and signal transducers the cell expresses. We previously identified fibronectin leucine-rich transmembrane protein (FLRT) family as a ligand of Unc5 proteins, a well-known Netrin receptors. FLRT2 is expressed in the cortical plate (CP) and inhibited migration of Unc5D+ cells in the subventricular zone (SVZ). The upper layer neurons in FLRT2 mutant mice showed earlier migration to CP, indicating the repulsive function of FLRT2. However, the behavioral phenotype of FLRT2 deficient mutant mice was unclear. Here, we comprehensively analyzed behaviors of Emx1 cre induced- FLRT2

conditional knock-out mice using the test battery, including rotarod, T-maze, Barns maze, fear conditioning, prepulse inhibition, tail suspension, forced swim, object location test, pattern separation test, open-field, light/dark transition, elevated plus maze, hot plate test and social interaction tests. Among these tests, we found that mutant mice showed significant enhancement of anxiety-like behaviors (light/dark transition and elevated maze tests), pain sensitivity (hot plate test) and social behavior (social-interaction test). Furthermore, exploratory locomotor activity was decreased (open-field and Y-maze tests). Next, we analyzed the amino acids contents in the brain by matrix-assisted laser desorption/ionisation (MALDI) imaging mass spectrometry. We found that serotonin content in the forebrain of FLRT2 cKO is higher than control mice. These results suggest that serotonin of forebrain might affect the behaviors of FLRT2 deficient mice resulting in increased social interaction.

Disclosures: **S. Yamagishi:** None. **F. Eto:** None. **Y. Shinoda:** None. **S. Ogawa:** None. **I. Yao:** None. **K. Takao:** None. **T. Miyakawa:** None. **K. Sato:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.13/S15

Topic: F.03. Neuroendocrine Processes

Support: Shanghai Science and Technology Committee 17ZR1403300
The National Natural Science Foundation of China 31800987

Title: Alterations of estradiol-induced histone H3 acetylation in the preoptic area and anteroventral periventricular nucleus of middle-aged female rats

Authors: *Y. SUN, W. XU, J. HUANG, L. LI, X. ZHANG, Y. WANG;
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Abstract: Histone acetylation has recently been implicated in gene expression and estradiol (E2) actions in the hypothalamus. This study aims to determine the characteristic of histone acetylation in the hypothalamus under E2 positive feedback to understand the mechanism underlying alterations of gene expression and LH surge dysfunction in female reproductive aging. Young and middle-aged female rats were ovariectomized (OVX) and treated with hormone or oil once per day for two days. At the time of the expected LH surge, blood samples were taken for LH assay. The anterior and posterior hypothalami were dissected, histone H3 acetylation was measured using Western blotting. Independent groups of animals were perfused, GnRH neuron co-localized with c-Fos in the preoptic area (POA) and acetylated histone H3 cells in the POA and anteroventral periventricular nucleus (AVPV) were quantified. *Esr1* target genes including *Kiss1* and *VGluT2* and genes known as *Esr1* coregulators with histone

acetyltransferases (HATs) activity expression in the anterior hypothalamus were evaluated. Our results show that in the young females, E2 markedly increased histone H3 acetylation in the anterior hypothalamus especially in the POA and AVPV, coincidence with an increased GnRH neuron expressing c-Fos in the POA. However, E2-induced alterations of histone H3 acetylation in the anterior hypothalamus were absent in middle-aged females. The histone H3 acetylation immunoreactive cells were decreased in the POA and were absent of change in the AVPV of middle-aged females, associated with attentuated LH release, reduced GnRH expressing c-Fos as well as down-regulation of *Kiss1* and *VGluT2* mRNA expression. E2 induces significant decreases of *Ncoa2* and *Crebbp* mRNAs expression in young but not middle-aged anterior hypothalamus. Taken together, these data suggest that alterations of histone H3 acetylation in the POA and AVPV and the missing responsiveness of *Esr1* coregulators *Ncoa2* and *Crebbp* to E2 in the middle-aged anterior hypothalamus may partially contribute to E2 target gene expression changes and GnRH neuron activation decline and consequently lead to LH surge dysfunction in female reproductive aging.

Disclosures: Y. Sun: None. **W. Xu:** None. **J. Huang:** None. **L. Li:** None. **X. Zhang:** None. **Y. Wang:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.14/S16

Topic: F.03. Neuroendocrine Processes

Support: NIH R01DA042351
University of Michigan Transgenic Mouse Core

Title: Introduction of the human PCSK1 mutation G209R into mice leads to frequent neonatal mortality and dwarfism in surviving adults

Authors: S. GAHLOT[1], M. SHAKYA[2], I. LINDBERG[2], *M. J. LOW[1];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Dept of Anat. and Neurobio., Univ. of Maryland Dept. of Anat. and Neurobio., Baltimore, MD

Abstract: Prohormone convertase 1/3 (PC1/3), encoded by the *PCSK1* gene, performs the initial processing step of a variety of prohormone and neuropeptide precursors to their bioactive forms. While hypomorphic mutations in *PCSK1* can disrupt precursor processing and lead to metabolic and hormonal phenotypes, other common nonsynonymous SNPs are associated with obesity risk. One rare human SNP causing a G209R mutation produces a severe neonatal malabsorption syndrome followed later by additional syndromic features of *PCSK1* malfunction. The goal of the current study was to mimic this catalytically dead mutation in a mouse model to investigate

the mechanisms underlying the evolving human phenotypes. A G209R (gga to aga) point mutation was introduced into exon 6 of mouse *Pcsk1* by homology-directed repair using CRISPR/Cas genome engineering. Two heterozygous C57BL/6J founders carrying the correctly mutated site were identified by sequencing of a PCR-amplified DNA fragment encompassing exon 6. Intercrosses of G209R heterozygous N2 mice revealed early postnatal lethality of most homozygous R/R pups. Fifty-six live pups of both sexes, collected at postnatal days one or two from 10 litters, had the following genotypes: 27% G/G, 41% G/R and 32% R/R. Bodyweights were identical across the three genotypes, and stomachs of all pups had milk, indicating suckling activity. Plasma corticosterone levels were normal; however, mean blood glucose levels were significantly lower in homozygous R/R (62 ± 6 mg/dl) vs. G/G wildtype (90 ± 3 mg/dl) pups. Insulin levels were much more variable in the R/R pups (range 0.1 to 3.5 ng/ml) than in the other genotypes (0.1 to 0.9 ng/ml); however, there was a significant direct correlation between insulin and glucose levels (linear regression: r^2=0.45, *P*=0.008) only for the R/R pups. Five male R/R pups survived past one week, were severely dwarfed, but otherwise appeared healthy up to age 16 weeks. In summary, the phenotypic effects of the missense G209R mutation in mice are more severe than that reported previously for a *Pcsk1* null allele. However, the dwarfism phenotype of the few mice surviving into adulthood resembles that of the *Pcsk1* null mutants and is likely caused by abnormal processing of the hypothalamic GHRH prohormone. Additional studies, including effects on hypothalamic and gastrointestinal precursor processing and cellular ER stress pathways, are needed to identify the specific cause of the early postnatal mortality seen in the G209R mouse.

Disclosures: S. Gahlot: None. **M. Shakya:** None. **I. Lindberg:** None. **M.J. Low:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

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Program #/Poster #: 499.15/S17

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Training Grant T32CA009338
OSU COM

Title: Estrogen signaling modulation by mammary tumors: A role in cognitive dysfunction?

Authors: *K. L. G. RUSSART, L. STREHLE, V. BURCH, A. OATES, A. THOMAS, A. LAHOUD, J. KAUR, L. PYTER;
Ohio State Univ., Columbus, OH

Abstract: Cognitive deficits are a common complaint in breast cancer patients. Recent studies indicate the cause of cognitive impairment is likely multi-modal; chemotherapy, tumor biology,

surgery, stress, and hormones are all potential contributors. The majority of breast cancer patients are post-menopausal, and therefore have low levels of circulating estrogens. Additionally, many survivors are treated with long-term (>20 years) estrogen-reducing pharmaceuticals. Therefore estrogens, which are involved in modulation of cognition, might be involved in cancer-related cognitive impairment. We investigated the effects of a breast cancer tumor and its removal on cognitive performance and serum estradiol-17β (E_2) in a mouse model of breast cancer. Intact and ovariectomized mice were given tumors, and half of the tumors were subsequently resected (survivors). OVX mice performed more poorly than intact mice during cognitive tasks such as the novel object recognition and fear conditioning tests, and the presence of a tumor reduced performance further. Uteri weighed less and serum E_2 concentrations were reduced with ovariectomy, but E_2 was modulated with a tumor and tumor resection. Intact mice with tumors had disrupted estrous cycles; they spent more days in diestrus (and fewer days in metestrus), and some tumor-bearing mice discontinued cycling. Lastly, hippocampal expression of estrogen receptor α, pro-inflammatory *Il-1β* and *Il-6*, and synaptogenesis genes *Syn* and *Bdnf* was modulated with tumors and tumor resection. Thus, neural inflammation and synaptic plasticity, both estrogen-mediated events, are potential contributors to the observed cognitive dysfunction.

Disclosures: K.L.G. Russart: None. **L. Strehle:** None. **V. Burch:** None. **A. Oates:** None. **A. Thomas:** None. **A. Lahoud:** None. **J. Kaur:** None. **L. Pyter:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.16/S18

Topic: F.02. Behavioral Neuroendocrinology

Support: Macao Science and Technology Development Fund, FDCT, Project 093/2017/A2
Macao Science and Technology Development Fund, FDCT, Project 011/2014/A1

Title: Temporal dynamics of the behavioral and endocrine response to an aggressive challenge in wild-type and fighter strains of the Siamese fighting fish Betta splendens

Authors: *D. GONÇALVES, A. RAMOS, S. D. CARDOSO;
Univ. of St. Joseph, Macao, Macao

Abstract: Domestication usually encompasses taming the behavior of wild animals with a concomitant reduction in aggression. However, in a few species domestication has been associated with selection for high aggression, either by cultural or research purposes. One such example is the Siamese fighting fish Betta splendens, where males have been selected for winning dyadic fights in street contests, in a process that is thought to be going on for several

centuries. By comparing selected “fighter” strains with unselected wild-type counterparts, it is possible to identify the genetic, physiological and behavioral consequences of this prolonged selection process. Here, we show that selecting males for winning fights not only increases the frequency and intensity of aggressive behaviors, presumably because more aggressive males will tend to win fights, but also changes the structure of fights, revealed by differences in the temporal sequence of behaviors and fight duration. Further, the temporal dynamics of androgens secretion in plasma, hormones associated to the modulation of aggression in fish, differed between fighter and wild-type males, suggesting that selection for winners resulted in shorter endocrine response latencies. The androgen response to the aggression challenge was pronounced, although of a similar amplitude in both strains. The activation of the stress axis during fights, as measured by plasma cortisol levels, was not significant in either strains. However, fighters had significantly lower baseline cortisol levels than wild-types and low cortisol has been associated with high aggression in fish. Taken together, the results suggest that chronic low cortisol levels, a fast androgen response and changes in fight structure favor winning dyadic encounters in the context of staged fights in B. splendens.

Disclosures: D. gonçalves: None. **A. Ramos:** None. **S.D. Cardoso:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.17/DP09/T1

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: F.02. Behavioral Neuroendocrinology

Support: NSF Grant 1645170

Title: Viral-mediated transgenesis of MAOA and AVP increases territorial aggression in stickleback

Authors: *N. J. JAMES[1], A. BELL[2];
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Abstract: Establishing a causal relationship between genes and social behavior is challenging. Threespine sticklebacks are a classic system for the study of behavior, ecology, and evolution. They are one of the best studied behavioral systems, with well described intra-specific variation in aggression, antipredator behavior, and parental care. During the breeding season, male sticklebacks defend nesting territories and are highly aggressive toward territorial intruders. Previous studies, ranging from QTL to RNAseq, have identified hundreds of genes that are

differentially expressed in the brain in response to a territorial intrusion, but we know little about the mechanisms by which changes in their expression relate to territorial aggression.
Here, we use viral-mediated transgenesis to test the effects of candidate genes in the brain on territorial aggression. This method is appealing because it is flexible, fast, and allows us to compare individual behavior before and after transgenesis. Specifically, we tested the effects of two candidate genes, monoamine oxidase (MAOA) and arginine vasopressin (AVP), on aggressive behavior in male sticklebacks. Based on the literature, we predicted that overexpression of MAOA would reduce territorial aggression, whereas overexpression of AVP would increase territorial aggression. Aggression was measured relative to a control group of fish injected with a novel fluorescent (EYFP) protein.
Individuals' behavioral response to a territorial intruder was recorded on four occasions - two before injection and two after the construct reached peak expression. Sticklebacks received transcranial injections of mammalian homolog cDNA packaged in a replication-deficient Herpes Simplex Virus 1 carrier. Two injections to the anterior diencephalon resulted in broad expression throughout the brain. Expression levels of the candidate genes were confirmed using qPCR. As expected, the behavioral response of males in the control group to a territorial intruder did not differ before versus after injection.
Consistent with our hypothesis, animals injected with the construct causing overexpression of AVP were more aggressive in response to a territorial intrusion after injection relative to before. Surprisingly, animals overexpressing MAOA also showed higher levels of aggression in response to a territorial intruder. Overall, these results show that viral-mediated transgenesis is a promising method for testing the function of candidate genes in this system. Additionally, candidate gene selection is not limited to native genes: widely available mammalian plasmids successfully altered behavior.

Disclosures: **N.J. James:** None. **A. Bell:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.18/T2

Topic: F.02. Behavioral Neuroendocrinology

Support: FAPESP Grant nº 2018/24288-7
FAPESP Grant nº 2016/18667-0

Title: Hypothalamic activation after restraint stress and social stress in C57Bl/6 mice

Authors: *A. P. ALMEIDA, S. C. MOTTA;
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Abstract: Entrapment is typically related to aversive situations, and it can depend on only physical limits, like restraint stress, or more than one type of limits, like psychological and physical during social confrontation. In Wistar male rats, a septo-hippocampal-hypothalamic path is likely to respond to the environmental boundaries, contributing to the organization of defensive behaviours during different threats. In order to better understand defensive behaviours and how this can be modulated by entrapment in C57Bl/6 male mice, we intend to analyse if the structure relationed with this path is also mobilized in response to different threats, as in Wistar rats. For this, we have compared the pattern of juxtadorsomedial of lateral hypothalamic area (LHAjd) , the ventrolateral part of the ventromedial nucleus (VMHvl) and dorsal premammillary nucleus (PMd) activation of animals submitted to social defeat (n = 7), restraint stress (n = 5) and controls animals (n = 5). The activation was evaluated measuring the density of Fos-immunoreactive neurons of the selected brain regions. Univariate ANOVAs showed significant group effects for all hypothalamic sites analysed ($F(2, 42) = 31.91$; $p < 0.0001$). Using *post hoc* pairwise comparisons (Tukey HSD) we noted that, compared to the Control and Immobilized groups, Defeated animals up-regulated Fos expression in the VMHvl ($p < 0.0001$). In addition, density of Fos-labeled cell of LHAjd and PMd was significantly greater in the Defeated (LHAjd, $p = 0.0040$; PMd, $p = 0.0041$) and Immobilized (LHAjd, $p = 0.0256$; PMd, $p = 0.0101$) groups than in the Controls. As expected, the VMHvl - an element of the social responsive circuit responded only situations with social cues; and the PMd - which seemingly works as a key player for the expression of some of the defensive behavioural responses, was activated on both restraint and social stresses. In accordance to the observed in Wistar rats, LHAjd also responded in both situations, which is expected if LHAjd is conveying environmental restriction information from septo-hippocampal system to PMd. All this support our idea that a septo-hippocampal-hypothalamic path, responsive to social and physical restraint, is modulating defensive behaviours and have motivated us to realize more morphofunctional studies for establish this likely path.

Disclosures: **A.P. Almeida:** None. **S.C. Motta:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.19/T3

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH110212

Title: Sex differences in the effects of social status and fluoxetine treatment on aggression in Syrian hamsters

Authors: *D. A. VOISIN[1], V. MICHOPOULOS[2], K. L. HUHMAN[1], H. ALBERS[1];
[1]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Yerkes Natl. Primate Res. Ctr. and Dept. of Psychiatry and Behavioral Sci., Emory Univ., Atlanta, GA

Abstract: It has been proposed that phenotypes related to dominance and more active coping strategies are more resilient to disorders like anxiety and PTSD. While the underlying mechanisms of these disorders remain poorly understood, there are marked sex differences in their incidence in the population. Selective serotonin reuptake inhibitors (SSRIs) like fluoxetine are among the most widely prescribed drugs for the treatment of many of these disorders, yet basic research has shown that the effects of these drugs can be sex dependent. For example, in Syrian hamsters, injection of serotonin 1a agonists into the anterior hypothalamus reduces aggression in males and increases aggression in females. In the present study we investigated whether social status (dominant versus subordinate) influences the amount of aggression displayed by males and females towards a non-aggressive intruder placed in their home cage. We also determined that social status and sex alters the effects on aggression of fluoxetine injected IP. Here, we show that male dominants displayed more aggression than did male subordinates ($p<0.05$). In contrast, no status-related differences were observed in the amount of aggression displayed towards a non-aggressive intruder. In males, fluoxetine significantly ($p<0.05$) reduced the amount of aggression displayed by dominant males but had no effect on the duration of aggression displayed by subordinates. In females, by contrast, fluoxetine significantly ($p<0.05$) reduced aggression in subordinate females compared to controls but had no effect on aggression in dominant females. These data demonstrate that social status influences competitive aggression as well as the effects of fluoxetine on aggression in a sex-dependent manner. These data suggest that subordinate females, who may already be more susceptible to social stress-related insults may become less aggressive when using SSRIs, while dominant males who may have some intrinsic or acquired resilience to social stress may see this resilience reduced.

Disclosures: D.A. Voisin: None. **H. Albers:** None. **K.L. Huhman:** None. **V. Michopoulos:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.20/T4

Topic: F.02. Behavioral Neuroendocrinology

Support: NIH Grant MH109942
NIH Training Grant HD049336 ("Common Themes in Reproductive Diversity")

Title: Melatonin regulates seasonal variation in neurosteroid profiles and aggressive behavior in male Siberian hamsters

Authors: *K. M. MUNLEY, J. E. DEYOE, C. H. ADANIYA, A. M. NOWAKOWSKI, C. C. REN, G. V. MURPHY, J. M. REINHART, G. E. DEMAS;
Biol., Indiana Univ., Bloomington, IN

Abstract: Numerous studies across animal taxa have demonstrated a positive correlation between gonadal steroids and aggression during the breeding season. However, it is becoming increasingly clear that alternative neuroendocrine mechanisms, which are independent of circulating gonadal steroids, are critical in modulating aggressive behavior. Such mechanisms are particularly important for seasonally-breeding animals that are more aggressive during the short-day (SD) photoperiods of the non-breeding season, despite gonadal regression and reduced circulating steroid levels. While previous work from our lab suggests that the pineal hormone melatonin and the adrenal androgen dehydroepiandrosterone (DHEA) are important in facilitating non-breeding aggression in Siberian hamsters (*Phodopus sungorus*), it is unknown whether local changes in steroid hormone synthesis and metabolism within the brain are ultimately responsible for elevating aggression during the non-breeding season. To investigate the role of melatonin in mediating seasonal variation in neurosteroid profiles and aggressive behavior, we housed male hamsters in long days (LD) or SD, treated them with either timed melatonin or saline injections, and quantified aggression after 9 weeks of photoperiodic housing. Following behavioral testing, we assessed whether melatonin mediates seasonal changes in steroidogenesis by comparing circulating hormone levels and neurosteroid levels in regions of the social behavior network that are associated with aggressive or reproductive behaviors using liquid chromatography-tandem mass spectrometry (LC-MS/MS). LD hamsters administered melatonin (LD-M) exhibited SD-like levels of aggression. Interestingly, LD-M and SD animals reduced circulating DHEA and testosterone concentrations in response to an aggressive encounter, whereas LD animals elevated circulating androgen levels. Neurosteroid profiles will also be presented and compared across brain regions and seasonal phenotypes. Collectively, this study provides insight into how melatonin modulates the neuroendocrine circuits underlying seasonal aggression.

Disclosures: K.M. Munley: None. **J.E. Deyoe:** None. **C.H. Adaniya:** None. **A.M. Nowakowski:** None. **C.C. Ren:** None. **G.V. Murphy:** None. **J.M. Reinhart:** None. **G.E. Demas:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

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Topic: F.02. Behavioral Neuroendocrinology

Support: Macao Science and Technology Development Fund, FDCT, Project 093/2017/A2

Macao Science and Technology Development Fund, FDCT, Project 011/2014/A1

Title: Selection for aggression changes brain expression patterns in male and female Siamese fighting fish Betta splendens

Authors: *S. D. CARDOSO[1], A. RAMOS[1], M. HUAWEI[2], Q. JIANWEN[2], D. GONÇALVES[1]; [1]Univ. of St. Joseph, Macao, Macao; [2]Hong Kong Baptist Univ., Hong Kong, Hong Kong

Abstract: Dominance relationships within and between sexes are usually a characteristic trait of a species' social system and have implications for differentiated access to resources, predation, mating strategies, and life history patterns of both sexes. The expression of dominance is often linked to aggressive behavior and the response it elicits, but the proximate mechanisms (i.e. genetic, hormonal and neuronal) of this behavior are not yet well understood. Here we focused on the neurogenomic mechanisms mediating aggression in both males and females using the Siamese fighting fish *Betta splendens* as our model system. This species has been selected for fighting contests across several centuries in Thailand and other Asian countries, generating highly aggressive fighting strains of *B. splendens*, known as "plakat morh", that are notoriously different from their counterpart wild-types. This artificial selection procedure has presumably favored genetic variations that promote the phenotypic expression of traits that increase the probability of winning fights and presumably aggression. In this study, a strain of wild-types and a strain of fighters were reproduced under lab conditions for several generations and differences in behavior and in the brain transcriptome were compared between sexes and strains. As expected, when presented to an aggressive challenge, either a mirror image or an interacting conspecific, fighter males were more aggressive than wild-type males. Interestingly, these differences also occurred for females, although only males have been directly subject to artificial selection. Whole-brain gene expression analyses, using as a reference the *B. splendens* genome, revealed that the selection for aggression induced a markedly different neurogenomic baseline state and response to the challenge in fighters, as compared with wild-types. The study provides evidence on brain gene regulation associated with the expression of aggression and presents the first comparison of males and females for *B. splendens* strains, a promising species for the investigation of the proximate and ultimate mechanisms of aggression in vertebrates.

Disclosures: S.D. Cardoso: None. **A. Ramos:** None. **M. Huawei:** None. **Q. Jianwen:** None. **D. Gonçalves:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

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Topic: F.02. Behavioral Neuroendocrinology

Support: Strategic Priority Research Program of the Chinese Academy of Sciences (XDB02050002)
National Basic Research Program of China (2013CB835100)
National Science Foundation of China (31130067 and 31460262)
People's Government of Yunnan Province (2015HA0036)

Title: Corticosterone signaling and a lateral habenula-ventral tegmental area circuit modulate compulsive self-injurious behavior in a rat model

Authors: Y. GUO[1], ***X. TANG**[3], J. ZHANG[4], S. JIN[6], J. LI[3], L. DING[7], K. ZHANG[7], C. YANG[7], H. ZHOU[5], X. HE[8], F. XU[9], G. BI[10], L. XU[3], P. LAU[2];
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Abstract: Self-injurious behavior (SIB) is commonly observed in patients with neuropsychiatric disorders, as well as in nonclinical populations with stress-related mental-health problems. However, the exact circuitry mechanisms underlying SIB have remained poorly understood. Here, with a bilateral injection of muscimol into the entopeduncular nucleus (EP), we established a rat model of SIB. Following the muscimol injection, the male rats exhibited in a dose-dependent manner stereotypic self-biting behavior that lasted for hours and often resulted in wounds of various severities. The SIB was associated with an elevated level of serum corticosterone and could be exacerbated by enhancing the corticosterone signaling and, conversely, alleviated by inhibiting the corticosterone signaling. Activity mapping using c-fos immunostaining, combined with connectivity mapping using herpes simplex virus-based anterograde tracing from the EP and pseudorabies virus-based retrograde tracing from the masseter muscle, revealed the potential involvement of many brain areas in SIB. In particular, the lateral habenula (LHb) and the ventral tegmental area (VTA), the two connected brain areas involved in stress response and reward processing, showed a significant increase in neuronal activation during SIB. Furthermore, suppressing the LHb activity or modulating the GABAergic transmission in the VTA could significantly reduce the occurrence of SIB. These results demonstrate the importance of stress hormone signaling and the LHb-VTA circuit in modulating SIB resulting from EP malfunction and suggest potential targets for therapeutic intervention of SIB and related disorders.

Disclosures: Y. Guo: None. **X. Tang:** None. **J. Zhang:** None. **S. Jin:** None. **J. Li:** None. **L. Ding:** None. **K. Zhang:** None. **C. Yang:** None. **H. Zhou:** None. **X. He:** None. **F. Xu:** None. **G. Bi:** None. **L. Xu:** None. **P. Lau:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.23/T7

Topic: F.02. Behavioral Neuroendocrinology

Support: NINDS Grant NS034950
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NIMH Grant MH096220
Arnold O. Beckman Postdoctoral Research Fellowship

Title: Control of social status is distributed across androgen receptor paralogs in a cichlid

Authors: *B. A. ALWARD[1], **C. J. SKALNIK**[1], R. A. YORK[1], S. A. JUNTTI[2], R. D. FERNALD[1];
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Abstract: Adaptations to the social environment require integrative responses involving physiological and behavioral plasticity. The mechanisms underlying these types of plasticity remain to be established. Here, we investigate the role of androgen receptors in the control of social status in the African cichlid fish *Astatotilapia burtoni*, a genetically tractable model system in which the mechanistic basis of social plasticity can be studied. In *A. burtoni*, males compete for rank along a social hierarchy, wherein dominant (DOM) and non-dominant (ND) males differ markedly in the behaviors they perform and their physiological state. DOM males are brightly colored, aggressively defend territories, and actively court females. In contrast, ND males are drably colored and rarely perform aggressive or courtship behavior. DOM males also possess larger testes and higher circulating levels of sex steroid hormones such as androgens and estrogens compared to ND males. Importantly, social status in *A. burtoni* is in flux, as DOM and ND males can rapidly alter certain aspects of their physiology and behavior in response to changes in the social environment. To test the role of androgen signaling in regulating social status, we generated using CRISPR/Cas9 gene editing *A. burtoni* with non-functional androgen receptor-α (ARα) or ARβ. Adult wild-type and mutant males were housed for 6-10 weeks in "stable-DOM" tanks, which include numerous territories and several other males and females. Stable-DOM tanks reliably induce the full suite of physiological and behavioral traits that characterize social dominance. Males were then assayed in a social dyad paradigm, where their interactions with a smaller male and three females were recorded. We find that ARβ is necessary for DOM-typical bright coloration and large testes, but not necessary for DOM-typical behavior. In contrast, ARα is not required for DOM-typical coloration, but is required for DOM-typical behavior (aggressive and courtship displays) and reducing testes growth. Thus, we demonstrate that AR paralogs are required for distinct traits underlying social status. Moreover, our findings

suggest that social status in *A. burtoni* is highly dissociable, a feature that may facilitate efficient social decision-making.

Disclosures: B.A. Alward: None. **C.J. Skalnik:** None. **R.A. York:** None. **S.A. Juntti:** None. **R.D. Fernald:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.24/T8

Topic: F.02. Behavioral Neuroendocrinology

Support: MH109302

Title: CRISPR Cas9 generation and behavioral characterization of a syrian hamster V1a receptor knockout

Authors: *J. H. TAYLOR[1], J. C. WALTON[1], K. E. MCCANN[3], A. NORVELLE[1], Q. LIU[2], J. VANDER VELDEN[1], J. M. BORLAND[1], M. HART[2], C. JIN[2], K. L. HUHMAN[1], D. N. COX[1], H. ALBERS[1];
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Abstract: The advancement of CRISPR-Cas9 for genetic modification has made possible the generation of new knockout animal models. Syrian hamsters are an attractive target for CRISPR-mediated gene modification due to their widespread use in biomedical research, particularly as a model in preclinical studies of psychiatric disorders. . Numerous social behaviors in hamsters and other species are controlled by the nonapeptide neurochemical signal vasopressin and one of its receptor subtypes (V1aR). Notably, selective stimulation of V1aR increases inter-specific aggression and flank marking in male and female hamsters. Thus, we sought to disrupt the *AVPR1A* gene and to assess these two vasopressin-dependent behaviors. Hamster embryos were injected at the single-cell stage with Cas9 and gRNA targeting AVPR1A, producing hamsters carrying various mutant *AVPR1A*. Of these, a mosaic female produced offspring carrying an 11bp or a 10bp deletion, both at the start codon of *AVPR1A*. Radioligand binding assays showed little to no selective V1aR binding in knockout hamsters homozygous for the 11bp deletion or heterozygous for both deletion alleles, indicating that the function of AVPR1A was disrupted. When compared to WT and heterozygous (-11/WT or -10/WT) littermates, however, male and female knockout hamsters were more aggressive toward a same-sex conspecific ($p<.05$) and engaged in more odor-stimulated flank marking ($p<.01$). This behavioral result is in direct opposition to our prediction, given that we have demonstrated based on behavioral pharmacological data that the V1aR in the anterior hypothalamus facilitates these behaviors. These data suggest a novel hypothesis that *global* inactivation of V1aRs may not block the

expression of flank marking or aggression. Thus, we administered a selective V1aR antagonist into the cerebral ventricles of wildtype hamsters. As predicted, this treatment did not block aggression in male or female hamsters; additionally, the V1aR antagonist tended to increase flank marking in males (p=.067). These data demonstrate that V1aR activation is not required for the expression of flank marking or aggression in constitutive V1aR knockouts and suggest the possibility that there is V1a-mediated process outside the AH in wildtype hamsters that inhibits aggression and flank marking. Supported by NIH MH109302.

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Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.25/T9

Topic: F.02. Behavioral Neuroendocrinology

Support: Ministry of Science, Research and Art of the 'Land Baden-Wuerttemberg' (Germany), grant program: 'Development of alternative methods to prevent animal experiments, award number 33-7533.-6-1521/7/2

Title: Suffering from aggression? Use cage climbers in your mouse cage!

Authors: *M. A. VOGT[1], S. SERBA[1], R. PALME[2], S. CHOURBAJI[1];
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Abstract: While many neurobiological publications describe clear effects of enrichment on the animals' physiology and behavior in an experimental context, large-dimensional implementation in rodent facilities often lacks a systematic analysis of respective refinement measures. Here, we aimed at implementing a new and innovative tool to improve wellbeing without side effects. Thus, we focused on enrichment-induced changes in behavior and stress physiology especially emphasizing effects on data variability in male and female mice. For that purpose, recycled cage lids were formed and three types of shapes examined for different effects of different structures ('cage climber'):
1.) 'Triangle' Climber,
2.) 'Bridge' Climber and
3.) 'Round Arch' Climber.
The results demonstrate significant preferences of C57BL/6N mice for any of the three structures in comparison with a neutral object. Despite observable intense use of enrichment, there were no

behavioral alterations detectable in a test battery assessing anhedonia (sucrose consumption) locomotion (openfield, rotarod), exploration (novel object exploration), anxiety (dark-light box) and sociability as well as social memory. The structural supplement neither affected levels of fecal corticosterone metabolites nor general variability of data in both male and female mice. The only detectable effect was a 50% reducting in male aggression in cages equipped with 'round arch' type of enrichment in comparison to control cages with nest material only.To promote well-being of mice in a 3R-matched context, our study recommends the use of properly assessed structural enrichment, such as ‘cage climbers’ combined with nesting material to satisfy physical and thermal needs in the cage environment.

Disclosures: M.A. Vogt: None. **S. Serba:** None. **R. Palme:** None. **S. Chourbaji:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.26/T10

Topic: F.02. Behavioral Neuroendocrinology

Support: PEACE from Japan International Cooperation Agency

Title: The relationship between testosterone and isolation-induced aggressive behavior in male layer chicks

Authors: *S.-I. KAWAKAMI, Z. YAN;
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Abstract: Testosterone (T) is known to induce aggressive behavior, mainly in male animals. It has not been known, however, whether rearing conditions such as isolated- or grouped-raising affect T-induced aggressive behavior and whether isolation-induced aggressive behavior is T-dependent in male chickens. The present study, therefore, aimed to examine (Exp. 1) the relationship between blood T concentration and aggressive behavior in group- and isolation-raised male layer chicks which were castrated and subcutaneously implanted T-filled silactic tubes; (Exp. 2) the effects of flutamide (F), a non-steroidal antiandrogen, on isolation-induced aggressive behavior of the castrated chicks. The Exp.2 was carried out because blood T concentration in the castrated chicks, probably derived from adrenal gland, was approximately 24 pg/ml in our previous study and therefore it is impossible to exclude completely the effect of lower concentration of blood T on chicken aggression only by castration. In the Exp. 1, the testes were bilaterally removed and silactic tubes of various lengths filled with crystalline T were subcutaneously implanted at 14 days of age, and a social interaction (SI) test was performed at 32 days of age to quantitatively assess aggressive behavior of the isolation- or group-raised chicks. Total aggression frequencies (TAF) and aggression establishment rate (AER) were used

to evaluate aggressiveness of the chicks (J. Poult. Sci., 54: pp. 296-302, 2017). The results of the Exp.1 showed that the TAF and AER were high irrespective of the plasma T concentrations in the isolation-raised chicks, but that in the group-raised chicks, the AER significantly increased only when plasma concentration of T was approximately 47 pg/ml. In the Exp. 2, the chicks were divided into three groups as follows: 1) intact male chicks; 2) the castrated ones in which blank tube were subcutaneously implanted; 3) the castrated ones in which F-filled tubes were subcutaneously implanted. After implantation, the chicks were reared in isolation and the SI test was performed at 32 days of age. In the Exp. 2, castrated chicks showed lower AER as compared with that of intact male chicks, and F-implantation lowered AER of the castrated chicks. These results suggest that both testicular and non-testicular T promote isolation-induced aggressive behavior in the male layer chicks.

Disclosures: S. Kawakami: None. **Z. Yan:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.27/T11

Topic: F.02. Behavioral Neuroendocrinology

Support: F31MH114509 to JRM
NSF 16-505 to DLM

Title: Evidence that differential expression of estrogen receptor alpha is causal for alternative behavioral phenotypes in a polymorphic species

Authors: *J. R. MERRITT, D. L. MANEY;
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Abstract: The white-throated sparrow represents a powerful model for understanding the mechanisms underlying steroid-dependent behavior. In this species, two morphs differ with respect to both expression of estrogen receptor alpha (ERa) and sex steroid-dependent behaviors. Birds of the white-striped (WS) morph engage in higher levels of territorial aggression than those of the tan-striped (TS) morph. WS birds also show several-fold higher expression of ERa in nucleus taeniae of the amygdala (TnA), which is functionally homologous to the mammalian medial amygdala. In regression analyses, expression of ERa in TnA predicts territorial aggression even better than morph, plasma testosterone, or plasma estradiol (E2). Previously, we showed that administration of E2 rapidly facilitates aggression in WS, but not TS, birds, suggesting that the polymorphism in ERa could contribute to the behavioral polymorphism. Here, we tested the hypothesis that the differential effects of E2 on aggression are mediated by differential ERa expression in TnA. We used antisense oligonucleotides to knock down ERa

expression in TnA of WS and TS birds. Separate control groups of both morphs received scrambled oligos. We then administered a bolus dose of E2 and quantified aggression towards a conspecific 10 minutes later. The results in the control group were consistent with our previous study; E2 facilitated aggression in WS, but not TS birds. Knocking down ERa expression in TnA eliminated E2-induced aggression in WS birds, making their behavior more typical of TS birds. Additionally, individual differences in the expression of ERa, but not ERb, in TnA predicted the degree to which E2 facilitated aggression. Overall, our results are consistent with the hypothesis that ERa expression in TnA mediates the well-known morph difference in aggressive behavior in this species, and may contribute to the evolution of social behavior.

Disclosures: J.R. Merritt: None. **D.L. Maney:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.28/T12

Topic: F.02. Behavioral Neuroendocrinology

Title: Neurochemical phenotyping of dominance and submissiveness

Authors: *K. MURLANOVA[1,2], A. PINHASOV[1], I. MICHAELEVSKI[1], M. V. PLETNIKOV[2];
[1]Integrative Brain Sci. Ctr. - Ariel, Mol. Biol., Ariel Univ., Ariel, Israel; [2]Dept Psychiat & Behav Sci., Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: To determine the contributions of different monoaminergic neurotransmitter systems to the neurochemical mechanisms of dominant and submissive behaviors, we measured tissue content of major monoamines and their metabolites in Sabra mice that were selectively bred over 34 generations to exhibit strong and stable dominant (Dom) or submissive (Sub) behaviors in several tests for social interactions including Dominant-Submissive Relationship and Resident-Intruder tests. Using HPLC-ECD method, we assayed monoamine tissues concentrations in the prefrontal cortex (PFC), hippocampus (Hip), cerebellum (Cer) and brainstem (BS) of naïve 8-week-old male Dom and Sub mice (n=7). We have identified different patterns of alterations in the monoaminergic systems between Dom vs. Sub mice behavior driven by distinct social rank status. Compared to Dom mice, Sub animals had decreased levels of norepinephrine (NE) in PFC and Hip, 5-hydroxytriptamine (5-HT) in BS and elevated levels of dopamine (DA) in all tested regions, which was associated with decreased DA turnover in Sub mice. Decreased 5-HT level in BS was associated with increased 5-HT turnover in Sub mice. Our findings suggest that different patterns of monoamine brain regional tissue content in Dom and Sub mice may explain stable differences in their social behavioral features with potential relevance to major psychiatric disorders.

Disclosures: **K. Murlanova:** None. **A. Pinhasov:** None. **I. Michaelevski:** None. **M.V. Pletnikov:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

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Program #/Poster #: 499.29/T13

Topic: F.02. Behavioral Neuroendocrinology

Support: Swedish Research Council (2018-02480
Novo Nordisk Fonden
Swedish Brain Foundation
Strategic Research Programme in Diabetes at Karolinska Institutet
StratNeuro Karolinska Institutet

Title: Methylphenidate-mediated inhibition of dopamine transporter-expressing non-dopaminergic neurons in the mouse ventral premammillary nucleus that control aggression

Authors: *L. T. A. HEIKKINEN[1], C. BROBERGER[1,2];
[1]Dept. of Neurosci., Karolinska Institutet, Stockholm, Sweden; [2]Dept. of Biochem. and Biophysics, Stockholm Univ., Stockholm, Sweden

Abstract: A population of neurons in the ventral premammillary nucleus that can be identified through expression of the dopamine transporter ("PMv^{DAT} cells") have recently been shown to control aggression and social dominance in male mice. Despite the robust expression of DAT in these cells, however, studies indicate that they neither synthesize nor release dopamine. This unorthodox neurochemical profile suggests that DAT may have a non-canonical function in the PMv. Intriguingly, the non-selective DAT-inhibitor, methylphenidate (MPH), commonly prescribed for attention deficit hyperactivity disorder, has been reported to reduce aggressive behaviour in both animal models and in human patients. To address the cellular bases for these issues, we used whole-cell patch clamp recordings in acute hypothalamic slices from male juvenile DAT-tdTomato mice. Recent work has identified several membrane properties of PMv^{DAT} neurons that make them conducive to persistent, regenerative discharge. Bath application of MPH (500μM) suppressed several of these features. Thus, both the number of spikes during a depolarizing current pulse injection, as well as during rebound firing in response to hyperpolarization, were decreased by 50%. Paradoxically, and pertinent to the latter, the amplitude of the depolarizing "sag", commonly attributed to the hyperpolarization-activated mixed cation current (h-current) appeared to be increased. Furthermore, the repolarization after current injection was delayed, suggesting an action on A-type potassium currents. The successive decrease in action potential amplitude observed during a burst was also enhanced, indicating a faster onset of depolarization block. Curiously, these effects were not observed during bath

application of the DAT-selective antagonist, GBR-12783 (10μM). - Together, these data indicate that MPH can interfere with the recurrent excitation mechanisms operating within the PMv, suggesting a means whereby this drug may suppress aggression. The pharmacological profile of these actions indicate that underlying non-conventional transporter actions are involved. The behavioural implications of these findings are currently under investigation.

Disclosures: L.T.A. Heikkinen: None. **C. Broberger:** None.

Poster

499. Hormone Modulation of Behavior and Physiology II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 499.30/T14

Topic: A.10. Development and Evolution

Support: NSF IOS 1557451
NSF GRFP

Title: Effect of early-life knock-down of DNMTs and TETs on sex differences in cell type in the hypothalamus

Authors: *L. R. CORTES[1], C. D. CISTERNAS[2], N. G. FORGER[1];
[2]Neurosci. Inst., [1]Georgia State Univ., Atlanta, GA

Abstract: One type of sex difference in the brain involves differences in the number of cells expressing a particular marker. For example, females have more cells expressing estrogen receptor alpha (ERa) in the ventrolateral region of the ventromedial nucleus of the hypothalamus (VMHvl), while males have more cells expressing calbindin in the sexually dimorphic nucleus of the preoptic area (CALB-SDN). DNA methylation and hydroxymethylation are crucial for the differentiation of neuronal cell phenotype during development, and we hypothesize that they may also play a role in the sexual differentiation of cell phenotype. To test this, we first treated newborn mice with zebularine, a global inhibitor of DNA methyltransferases (DNMTs). Zebularine treatment had lasting effects on the number of cells expressing ERa and calbindin and reduced or eliminated sex differences in these markers (Mosley et al. 2019). DNA methylation and de-methylation are carried out by DNMTs (DNMT1, DNMT3b, and DNMT3a) and TET enzymes (TET1, TET2, TET3), respectively. We find that expression of these enzymes is much higher early in life compared to adulthood, and there are sex differences in the expression of all TETs and of DNMT1. To test whether these sex differences in enzyme expression underlie sex differences in cell phenotype, we used small interfering RNAs (siRNA) to down-regulate DNMT1/DNMT3a or TET2/TET3. We found that injecting 2 microliters of 400pmol siRNA into the ventricles of male and female pups on P5 leads to a robust (~40%) down-regulation of expression compared to animals given control siRNA. Animals will be sacrificed at weaning,

and we will determine whether neonatal DNMT or TET knockdown alters the number of cells expressing ERa in the VMHvl and medial POA and calbindin in the SDN-POA and bed nucleus of the stria terminalis.

Disclosures: L.R. Cortes: None. **C.D. Cisternas:** None. **N.G. Forger:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.01/T15

Topic: F.04. Stress and the Brain

Support: Academy of Finland
Åbo Akademi University

Title: JNK controls hippocampal circuit dynamics assessed by fiberphotometry in behaving mice

Authors: J. JOHN[1], N. TIWARI[2], P. HOLLOS[3], F. MARCHISELLA[3], V. FAGERHOLM[1], S. HUUSKONEN[4], *E. T. COFFEY[5];
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Abstract: Our lab has previously shown that inhibition of JNK solely in adult born granule cells of the dentate gyrus (DG) decreases anxiety-like behavior in mice (Mohammad et al, Mol. Psychiatry, 2018). To understand how the action of JNK in a sub-population of cells in hippocampus can influence behavior, we analyzed whether inhibition of JNK in hippocampal neurogenic niche cells altered neural activity of pyramidal neurons in CA3 and CA1 sub-regions. We used a customized retroviral inhibitor of JNK that expreses specifically in newly born DG granule cells and measured neural activity from CA3 or CA1 pyramidal neurons expressing a GCaMP6s reporter using fiberphotometry in behaving mice undergoing a battery of anxiety-inducing tests. We find that inhibition of JNK in adult born neurons of DG alters hippocampal circuit activity. Moreover, we show that activity of CA3 neurons is altered in a battery of behavior tests and when JNK is inhibited in DG, shows strong correlation with low anxiety traits. These results identify JNK as a molecular driver of circuit activity in hippocampus.

Disclosures: J. John: None. **N. Tiwari:** None. **P. Hollos:** None. **F. Marchisella:** None. **V. Fagerholm:** None. **S. Huuskonen:** None. **E.T. Coffey:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.02/T16

Topic: F.04. Stress and the Brain

Support: NSF-REU 2016-156038
NSF-HRD 1736019
NSF-OISE 2015-1545803

Title: Learning expression of neurophysiological stress markers in honey bees

Authors: *T. E. BLACK[1], O. FOFAH[2], T. GIRAY[3], C. I. ABRAMSON[1];
[1]Psychology, [2]Entomology, Oklahoma State Univ., Stillwater, OK; [3]Dept. of Biol., Univ. of Puerto Rico, Carolina, PR

Abstract: Stress is defined as any deviation form an organism's baseline levels. As such, introduction of new stimuli and information, such as in learning, can be defined as a stressor. A large body of research exists examining the role that stress plays in learning, but virtually none addresses whether or not learning itself is a measurable cause of stress. The current study used a shotgun approach to examine learning in conjunction with stress and interpret whether or not learning was a sufficient stressor to elicit a transcriptional change. Researchers examined changes in expression of ten stress related genes in various physiological systems in domesticated honey bees (*Apis mellifera*) as a result of exposure to an aversive conditioning task. Gene expression was explored using quantitative real time polymerase chain reaction. Results were analyzed using a series of ANOVA.

Disclosures: T.E. Black: None. **O. Fofah:** None. **T. Giray:** None. **C.I. Abramson:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.03/T17

Topic: F.04. Stress and the Brain

Support: NIH Grant MH119106
NIH Grant MH095972

Title: Parallel prefrontal-periaqueductal gray circuits mediate active and passive coping behaviors in response to stress

Authors: *S. B. JOHNSON[1], R. T. LINGG[2], T. D. SKOG[1], S. A. ROMIG-MARTIN[2], R. T. LALUMIERE[2], J. J. RADLEY[2];
[1]Interdisciplinary Neurosci. Grad. Program, [2]Dept. of Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: The behavioral, neuroendocrine, and autonomic features that constitute the stress response may be coordinated by higher-order brain regions and their projections to downstream effectors. Among these features, it has been widely held that active behavioral coping can have buffering effects on other aspects of the stress response. However, this idea has garnered little direct support and the mechanisms underlying this phenomenon remain obscure. Here we employed an optogenetic approach to probe the contributions of medial prefrontal cortical (mPFC) pathways to the midbrain periaqueductal gray (PAG), a prominent behavioral effector, on coping during the shock probe defensive burying test (SPDB). In this test, rats are exposed to an electrified probe mounted within their cage, whereby after receiving electric shock, they display both active (probe burying with cage bedding) and passive (immobility) coping behavior that is monitored over a 10-min period. We found that photoinhibition of the rostral mPFC-ventrolateral PAG pathway enhanced, and photoexcitation diminished immobility relative to controls ($p < 0.05$ for each), but these had no effect on burying. By contrast, we found that photoexcitation of the caudal mPFC-dorsal PAG pathway enhanced active coping (probe-burying, $p < 0.05$) while immobility remained unaffected. As activity in this pathway is sufficient to drive active coping behavior, we next interrogated whether activating it in a setting where rats are forced toward passive coping, i.e. by removing the cage bedding during SPDB, could have stress-buffering effects. In the no-bedding condition, rats deprived of active coping responses exhibited increased immobility, ultrasonic vocalizations, autonomic, and HPA output, whereas pathway activation rescued each of these effects. These results show that latent, stress-buffering effects of caudal PL-dorsal PAG photoexcitation are uncovered in situations where active coping is prevented. Together, these experiments provide support for separate mPFC-PAG pathways that impart distinct functional consequences during acute stress exposure. The rostral mPFC-ventrolateral PAG pathway may bias the animal away from passive responses, while the caudal mPFC-dorsal PAG pathway may support active responses and their attendant stress-buffering effects.

Disclosures: **S.B. Johnson:** None. **R.T. Lingg:** None. **T.D. Skog:** None. **S.A. Romig-Martin:** None. **R.T. LaLumiere:** None. **J.J. Radley:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.04/T18

Topic: F.04. Stress and the Brain

Support: NIH R15 MH107007

Title: Social dominance alters both coping style and stress resilience

Authors: *M. CANNON, E. GRAHAM, M. BURZINSKI, N. SAGARAD, M. COOPER; Psychology, Univ. of Tennessee, Knoxville, TN

Abstract: There are a great deal of individual differences in how humans and other animals cope with stress. Variation in coping strategies is linked to several environmental factors, including social dominance. The present study investigated whether coping responses predict the acquisition of social dominance in male and female Syrian hamsters, establishing dominance relationships alters the development of coping responses, and changing dominance status further modifies coping. We also examined whether social dominance alters behavioral responses to social defeat stress as well as markers of neural activity in the nucleus accumbens, such as deltaFosB. We hypothesized that maintenance of dominance relationships would increase proactive coping in dominants and reactive coping in subordinates. Also, we hypothesized that dominant, proactive coping animals would show less defeat-induced social avoidance and greater deltaFosB expression in the nucleus accumbens compared to subordinate, reactive animals. To establish dominance relationships, male and female hamsters were paired with a same-sex partner in daily aggressive encounters for two weeks. To assay coping responses before and after formation of dominance relationships, we tested animals in a series of behavioral tests, including open field, novel object exploration, elevated zero maze, light/dark transition, and Porsolt forced swim. Finally, to measure stress susceptibility we exposed subjects to acute social defeat stress and subsequent social interaction testing. We found that after establishing social dominance, females spent more time in the light area of a light/dark transition test and approached a novel object more quickly than subordinate females, which suggests that establishing social dominance promotes proactive coping in female hamsters. Interestingly, when dominant females lost their dominance status they also lost their proactive coping responses. Contrary to our prediction, we found that dominant females showed increased social avoidance after defeat, which suggests that proactive coping does not promote stress resilience in female hamsters. We are currently testing male hamsters to investigate potential sex differences in coping responses and stress susceptibility. We are also quantifying deltaFosB expression in the nucleus accumbens in both females and males. These preliminary findings indicate that social dominance modulates both

coping responses and stress susceptibility and will address potential sex-differences and cellular mechanisms.

Disclosures: M. Cannon: None. **E. Graham:** None. **M. Burzinski:** None. **N. Sagarad:** None. **M. Cooper:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.05/T19

Topic: F.04. Stress and the Brain

Support: NIH R15 MH107007

Title: The effects of minocycline on acute defeat-induced social avoidance and microglial activity in the hamster vmPFC

Authors: *T. T. CLARITY[1], A. GRIZZELL[2], M. A. COOPER[2];
[1]The Univ. of Tennessee, Knoxville, Knoxville, TN; [2]Dept. of Psychology, Univ. of Tennessee, Knoxville, TN

Abstract: Neuroinflammation is a key risk factor in the etiology of stress-related psychopathologies. Exposure to social stress in rodents can increase activation of microglia, the brain's resident immune cells. The ventral medial prefrontal cortex (vmPFC) is a limbic region involved in top-down regulation of behavior and emotion, and has been implicated in resilience to traumatic stress. We and others have shown that disruption of vmPFC activity contributes to enhanced behavioral susceptibility to acute traumatic stress. However, it is unknown whether microglia contribute to such susceptibility. This study seeks to determine whether acute stress induces microglial activation in the vmPFC and, moreover, whether systemic administration of the microglial inhibitor, *minocycline*, reduces acute social defeat-induced social avoidance. Adult male Syrian hamsters were treated with *ad libitum* minocycline in drinking water (4 mg/ml; 130 mg/kg/day) starting 48-hours prior to stress (Day 1) and continuing until euthanasia 48 hours following stress (5 days total). On Day 3, minocycline and water-drinking controls were exposed to acute social defeat stress, which consisted of three 5-minute aggressive encounters in the home cages of three novel resident aggressors at 5-minute inter-trial intervals. On Day 4, defeat-induced social avoidance was assessed using conditioned defeat (CD) and social interaction (SIT) tests, which were counterbalanced across all treatment levels and spaced with 30-minute inter-assay intervals. On Day 5, animals were euthanized and brains extracted for immunolabeling of the microglial activation markers ionized calcium-binding adaptor protein (Iba-1) and Cluster of Differentiation 68 (CD68). Preliminary results suggest that acute social defeat increases Iba-1 expression in the vmPFC. We are currently using an amino cupric silver

stain to determine whether social defeat increases cellular degeneration. Also, ongoing experiments are testing the effects of minocycline treatment on microglial activity and morphology in the vmPFC and defeat-induced social avoidance. Given that vmPFC neuronal activity is necessary for protection against the adverse effects of stress, it is important to determine whether acute defeat-induced neuroinflammation in the vmPFC contributes to social avoidance. Overall, this study addresses whether halting microglial activity during acute social defeat protects vmPFC anatomical integrity and restores behavioral function, and might serve as a novel approach for pharmacological interventions used to treat traumatic stress exposure.

Disclosures: T.T. Clarity: None. **A. Grizzell:** None. **M.A. Cooper:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.06/T20

Topic: F.04. Stress and the Brain

Support: NIH R15 MH107007
UTK Graduate School Student/Faculty Award
UTK Office of Research Fellowship

Title: Microglial contributions to acute stress-induced perturbations of the vmPFC in male Syrian hamsters

Authors: *A. GRIZZELL[1], T. T. CLARITY[3], M. A. COOPER[2];
[2]Dept. of Psychology, [1]Univ. of Tennessee, Knoxville, TN; [3]The Univ. of Tennessee, Knoxville, Knoxville, TN

Abstract: The ventromedial aspect of the prefrontal cortex (vmPFC) plays a particularly important role in mediating resilience to acute and chronic psychological stress. Accordingly, work in our laboratory has shown that vulnerability to an acute social defeat stressor, such as that conferred by the maintenance of a subordinate social status, is associated with reduced neuronal activity in the vmPFC. Similarly, pharmacological inhibition of vmPFC projection neurons via muscimol attenuates the stress resistance conferred by a dominant social status. It is unknown what factors disrupt vmPFC recruitment in vulnerable populations, though recent findings suggest that excessive innate immune function could be implicated. In a series of studies, we sought to determine whether an acute social defeat stressor drives vmPFC microglial activity in a manner that contributes to status-dependent, stress-induced social avoidance. In Experiment 1, we identified whether acute social defeat primes an enhanced microglial response to a subsequent immune challenge [systemic lipopolysaccharide (LPS) injections]. We immunolabeled ionized calcium binding adaptor molecule (Iba-1) and CD68, a marker of

phagocytic activity following social defeat and/or LPS treatment and performed morphometric analysis of microglia in the vmPFC. Using similar immunolabeling techniques in Experiment 2, we sought to determine whether microglia activity was attenuated with systemic *minocycline* and, moreover, whether such treatment reduced acute social defeat-induced social avoidance in the conditioned defeat and social interaction tests. In Experiment 3, we sought to determine whether the development and maintenance of a subordinate social status for 14 days leads to greater vmPFC microglial recruitment and cellular degeneration in a manner correlated with acute defeat-induced social avoidance. Preliminary results suggest that acute defeat does indeed increase expression of Iba-1 as well as enhance ramification of microglial processes. Overall, this findings suggest that neuroinflammation in the vmPFC increases behavioral susceptibility to acute traumatic stress.

Disclosures: A. Grizzell: None. **T.T. Clarity:** None. **M.A. Cooper:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.07/U1

Topic: F.04. Stress and the Brain

Title: Chronic social defeat stress to adolescent mice induces anxiety-like behavior with reduced oligodendrogenesis

Authors: *T. SHIMIZU, A. ISHIDA, N. TAJIRI, H. HIDA;
Dept. of Neurophysiol. and Brain Sci., Nagoya City Univ., Grad. Sch. of Med. Sci., Nagoya, Aichi, Japan

Abstract: Myelination is dependent on neuronal activity and is modulated by various environmental changes in postnatal mice. Recent studies demonstrate that the myelin remodeling is involved in motor learning and social interaction. Our previous paper revealed that the average length of the myelin sheath formed by individual oligodendrocytes changed depending on sensory-input deprivation of neuronal axons. To investigate neuron-glial interactions and glial cell property itself in higher brain function and neurological disorders, we challenged to know whether psychosocial experience during adolescent period influences oligodendrocyte generation or its property using chronic social defeat stress to adolescent mice, a model for the examination of stress-related disorders in rodents. The socially defeated mice showed more anxiety-like behavior in the open field. The social defeat stress to adolescent mice led to decrease in the number of newly-born oligodendrocytes in the prefrontal cortex and in the number of PLP+ mature oligodendrocytes in the corpus callosum. In both of these regions of socially defeated mice, the number of BrdU-incorporated CC1-positive mature oligodendrocytes was also decreased. To assess whether oligodendrocyte remodeling plays roles in the anxiety-like

behavior caused by the social defeat stress, we applied drug modulating oligodendrocyte generation to socially defeated mice. We found that the drug treatment rescued the behavioral abnormalities, suggesting that the promotion of oligodendrogenesis can ameliorate depressive symptoms by the social defeat stress. Taken together, these findings suggest that oligodendrocyte remodeling under psychosocial environments plays important roles in mental disorder.

Disclosures: **T. Shimizu:** None. **A. Ishida:** None. **N. Tajiri:** None. **H. Hida:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.08/U2

Topic: F.04. Stress and the Brain

Support: This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001

Title: Distinct environmental stress response of mice with high and low immobility traits through the analysis of ultrassonic vocalization and chronic unpredictable stress exposure

Authors: *T. M. REIS-SILVA, A. C. S. SAMPAIO, P. S. RODRIGUES, M. C. GALVAO, E. P. SILVA, N. MOREIRA, L. S. MEDEIROS, K. E. KIATAQUI, M. M. BERNARDI; Post-Graduate Program of Envrn. and Exptl. Pathology, Paulista Univ., Sao Paulo, Brazil

Abstract: This study evaluated the response of high and low stress reactivity mice in the chronic unpredictable stress protocol to better understand and access possible biological mechanisms associated with the stress and resilience response. For this, 57 Swiss male mice with high (HI) and low immobility (LI) traits selected in the tail suspension test (TST), a screening protocol for antidepressant drugs, underwent 3, 10 and 21 days of chronic unpredictable stress. Behaviour analyses in the dark/light box were assessed and adrenal glands collected. During the TST, an ultrasonic vocalization (USV) test was also performed. Significant differences were determined by student t test and two-way ANOVA when pertinent. Our results show an increased frequency of rearing in the light zone after 10 days of stress [F (2, 23) = 9.176; P=0.0012] of LI group while HI displayed increased rearing frequency after 3 and 10 days and decreased frequency after 21 days [F (2, 23) = 7.458; P=0.0032] was observed. No differences in anxiety-like behaviour were observed. Adrenal weight of LI and HI group was elevated after 3 days of stress [F (1, 46) = 5.489; P=0.0235] when compared to 10 and 21 days. Regarding USV, HI animals presented elevated time (t test p=0.0006) and frequency (t test p=0.0045) of 22KHZ vocalization compared to LI group, revealing an aversive disposition to the TST inescapable stress. A previous work of our group showed rearing and corticosterone differences between HI and LI mice after restraint stress (Reis-Silva et al., 2019) and how those traits may be linked to

resilience response. Here, we suggest that the rearing response variation may also indicate changes in norepinephrine levels in areas such as the *locus coeruleus* and adrenal differences may refer to a distinct neuroendocrine activity via the hypothalamic-pituitary-adrenal axis. Finally, the USVs of 22 KHZ indicate a distinct sensibility to environmental stress between behaviours. We propose that animals of HI display a more sensibility to stress whereas LI resemble traits of stress resilience.

Disclosures: T.M. Reis-Silva: None. **A.C.S. Sampaio:** None. **P.S. Rodrigues:** None. **M.C. Galvao:** None. **E.P. Silva:** None. **N. Moreira:** None. **L.S. Medeiros:** None. **K.E. Kiataqui:** None. **M.M. Bernardi:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.09/U3

Topic: F.04. Stress and the Brain

Title: Perception of beauty during and after stress: The ugly becomes less uglier

Authors: *R. K. NARAYAN[1], A. KUMAR[1], V. PAREEK[2];
[1]Anat., All India Inst. of Med. Sci., Patna, India; [2]Computat. Neurosci. and Neuroimaging Div., Natl. Brain Res. Ctr., Manesar, India

Abstract: Introduction: Beauty lies in the eyes of the beholder', a paraphrase of a statement by Greece philosopher Plato, has often found its ground in the empirical studies. Though, how perception of the beauty changes during stress has been scarcely investigated until yet. We selected a paradigm of examination stress to investigate this question.
Materials and Methods: Ninety-one 1st professional MBBS students (72 males, 19 females) were presented with four types of pictures grossly representing three variations in perception of beauty: 1& 2-human figures toned with sexual fervour: that of a youthful man and a youthful woman, 3-the sex neutral aesthetic perception: a scene of nature, and 4-the ugliness: a human with an aggressive tumor on face) at the time of Anatomy viva voce examination, and 10 days after it. The participants were asked to evaluate the attractiveness of each picture with an ascending scale of marks ranging from 0 to 10.
Results: There were no distinct variances in the scores for the pictures during and after examination except that representing the ugliness. About 50% of the participants, irrespective of the gender, had given higher score for this picture in the post examination evaluation (which was considered free of stress) which meant they found it less ugly when were supposedly free of stress.
Discussion: The beauty is largely a subjective perception which may vary with the physiological conditions of the subject. Professional examinations are considered as stressful, which may

induce transient neuroendocrine changes, consequently may alter the aesthetic perception of the individuals. Though, direct literature evidence is scarce supporting increased sense of ugliness, an increase in the disgust sensitivity is known during stress, which closely relates to it. The altered perception of beauty during stress may have applied importance in aesthetic decision making during stressful conditions.

Disclosures: R.K. Narayan: None. **A. Kumar:** None. **V. Pareek:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.10/U4

Topic: F.04. Stress and the Brain

Support: National Natural Science Foundation of China (Grant 81671338)

Title: Role of Kalirin-7 in the mPFC in depression-like behaviors

Authors: C. WANG, *X. MA;
Shaanxi Normal Univ., Xi'an, China

Abstract: Depression is a common and severe psychiatric disorder, but the underlying mechanisms are still not entirely clear. Alterations in the structure and function of dendritic spines are associated with psychiatric diseases. The medial prefrontal cortex (mPFC) plays a critical role in the integration of cognitive and emotionally relevant information. Kalirin-7 (Kal-7), a major isoform of Kalirin in adult rodent brain, plays an essential role in the regulation of dendritic spine formation and synaptic plasticity. Therefore, this study was designed to investigate the effect of Kalirin in the mPFC on depressive-like behaviors using chronic unpredictable mild stress (CUMS), an animal model of depression. We showed that CUMS-induced depressive-like behaviors were accompanied by a decrease in Kal-7 levels in the mPFC in rats, which is consistent with the spine loss in this area. This finding raised our hypothesis that kalirin plays a critical role in CUMS-induced depression-like behaviors. The following experiment was designed to test this hypothesis.
Adults Sprague-Dawley male rats were divided into two groups: Kalirin knockdown and control (n=16), and an adeno-associated virus (AAV) encoding GFP-Kal-7 shRNA or scrambled shRNA was injected into their mPFC, respectively. Expression of Kal-7 shRNA resulted in a decrease in Kal-7 expression in GFP positive neurons of the mPFC compared with the mPFC neurons expressing scrambled shRNA.
Behavioral tests showed that, Kal-7 shRNA-mediated decrease in the level of Kal-7 induced depressive-like behaviors characterized by a decrease in sucrose preference ($p=0.005$) , rearing times ($p=0.001$) and time in center area(%) ($p=0.028$) in open field test, and an increase in

immobility time in tail suspension test (p=0.005). Depression-like behaviors induced by decreased Kal-7 level were accompanied by a marked decrease in spine density in spine density (p<0.001) and alterations in the morphology of dendritic spine in the mPFC. Western blot analysis showed that the levels of NR2B and GluA1 were significantly reduced (p=0.001, p=0.003) in the mPFC expression Kal-7 shRNA in comparison with the control group expressing scrambled shRNA. This study showed that reduced expression of Kalirin-7 in the mPFC contributes to depressive-like behaviors induced by CUMS.
Acknowledgement: this research was supported by the National Natural Science Foundation of China (Grant 81671338)

Disclosures: C. Wang: None. **X. Ma:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.11/U5

Topic: F.04. Stress and the Brain

Support: DFG - SFB1193

Title: Mice susceptible to chronic stress display a broadening of orientation tuning in microcircuits of the primary visual cortex

Authors: *H. BACKHAUS[1], N. BUERGER[1], P. KAPLICK[1], A. STROH[1,2];
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Abstract: Resilience towards chronic stress may not only be reflected in regions such as the dmPFC or VTA, but also in cortical areas not directly implicated in higher order behavior such as the primary visual cortex. Indeed, mounting evidence suggest, that stress resilience might be encoded already in the ability of an organism to differentiate between stimuli. To explore this hypothesis, we conducted two photon calcium imaging in layer II/III of visual cortex in mice previously categorized in terms of their response to chronic stress. We first submitted 8-week-old BL6 mice to a chronic social defeat paradigm, where the animals are exposed to physical attacks of a conditioned aggressor CD1 mouse for 10 consecutive days. Afterwards, the mouse remains in the same cage as the aggressor, but the aggressor is now physically separated, unable to attack. We classified the animals in resilient and susceptible subgroups by measuring the time spent in close proximity to the aggressor in a Social Interaction Test: Resilient mice continue to explore the aggressor that is safely kept in a mesh, whereas susceptible mice tend to avoid the vicinity of the aggressor. Upon implantation of a chronic optical window and the injection of the calcium indicator GCaMP6f, we conducted video-rate microcircuit imaging in resilient vs susceptible

awake mice, placed head-fixed on a jet-ball allowing for assessing locomotion. Mice were subjected to static and drifting grating stimulations in a virtual reality setting. Specifically in the susceptible mice, in excitatory neurons in layer II/III of primary visual cortex, we identified an increase of spontaneous, task-free, activity, both reflected in an increase of the number of spontaneous active neurons, as well as in the frequency of calcium transients. Upon grating stimulation, susceptible mice exhibited a significantly broader orientation tuning compared to their resilient litter mates. These findings imply that resilient and susceptible behavior is already reflected in neuronal activity patterns in primary sensory cortical areas. Indeed, susceptible mice might be less able to discriminate between threatening and safety cues, also at least partially based on their inferior perceptual abilities that are mediated by primary cortical areas.

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Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.12/U6

Topic: F.04. Stress and the Brain

Support: NIDA Grant 1R15 DA044500-01A1

Title: Oxytocin intranasal administration promotes exercise and decrease anxiety-like behaviors in rats

Authors: *P. A. MUÑOZ RODRÍGUEZ, L. G. RODRÍGUEZ SANTOS, W. NORZÉ, A. P. RAMOS ROLÓN, V. S. ENCARNACIÓN CORTES, F. M. GONZÁLEZ HERNÁNDEZ, E. OLMEDO LÓPEZ, C. S. MALDONADO-VLAAR;
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Abstract: Oxytocin (OT) is a neuropeptide primarily synthesized in the hypothalamus associated with social behaviors, stress responses, and drug addiction. Previous work from our laboratory showed a cross-talk between the endocannabinoid system (ECS) and OT receptors within the mesolimbic system to modulate anxiety behavior. Studies have demonstrated how ECS is crucial for voluntary wheel running performance. As a model for exercise, voluntary wheel running is endowed with anxiolytic properties due to increases in serum endocannabinoid concentrations. The purpose of the present study was to examine: (A) whether OT enhances voluntary wheel running behavior and potentiates the anxiolytic properties of exercise in adults male Sprague-Dawley rats and (B) characterize possible pathways mediating this effect within the mesolimbic system by assessing changes in OT and CB1 receptors expression. Rats were divided into two groups, the first group received intranasal infusions of OT 1 μg /μl, 10 μl or vehicle in each nostril before exposed to the running wheel two hours daily for 10 consecutive days. The second

group received the same dose of OT or vehicle and was not exposed to the running wheel. Results showed a tendency to increase wheel running behavior in rats treated with OT compared to the vehicle group. Results also showed the anxiolyticeffects of OT in sedentary rats were higher than the rats exposed to exercise by using Elevated Plus Maze (EPM). Further biochemical studies will examine cross-talk between OT and the endocannabinoid system as mediators of exercise performance and the implications it can have as a treatment on drug addiction, sedentary lifestyle and anxiety behaviors.

Disclosures: **P.A. Muñoz Rodríguez:** None. **L.G. Rodríguez Santos:** None. **W. Norzé:** None. **A.P. Ramos Rolón:** None. **V.S. Encarnación Cortes:** None. **F.M. González Hernández:** None. **E. Olmedo López:** None. **C.S. Maldonado-Vlaar:** None.

Poster

500. Behavioral Responses to Stress

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 500.13/U7

Topic: F.04. Stress and the Brain

Support: NIMH R21 Award (MH116263)
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Colorado Department of Public Health and Environment (CDPHE; grant number DCEED-3510)
Alfred P. Sloan Foundation (grant number, G-2016-7077)

Title: Neural mechanisms underlying stress-resilience effects of by immunization with mycobacterium vaccae in rats

Authors: *C. A. ZAMBRANO[1], M. G. FRANK[2], H. M. D'ANGELO[2], K. M. LOUPY[1], S. F. MAIER[2], C. A. LOWRY[1];
[1]Dept. of Integrative Physiol., Univ. of Colorado, Boulder, CO; [2]Dept. of Psychology and Neurosci., Univ. of Colorado Boulder, Boulder, CO

Abstract: Anxiety disorders and trauma- and stressor-related disorders are the most commonly occurring mental disorders, with estimated lifetime prevalence as high as 25%. Evidence suggests that inappropriate inflammation may be a risk factor for anxiety disorders, as well as

trauma- and stressor-related disorders, such as posttraumatic stress disorder (PTSD). Several studies have now demonstrated that psychobiotic treatments such as *Mycobacterium vaccae* (*M. vaccae*) are anxiolytic and induce a stress resilient phenotype. This induction of a stress resilient phenotype occurs, in part, through enhanced immunoregulation. We have recently found that administration of a heat-killed preparation of the anti-inflammatory and immunoregulatory bacterium, *M. vaccae* (NCTC 11659), a saprophytic bacterium found in soil, water, and mud, increases hippocampal expression of the anti-inflammatory cytokine interleukin 4 (IL-4) and IL-4-responsive genes, including CD200R1 and CD206, and prevents stress-induced microglial priming and anxiety (Frank et al., 2018, *Brain, Behavior, and Immunity*, 73, 352-363). Our goal here was to study the neural mechanism(s) involved in the effects of *M. vaccae* on hippocampal gene expression implicated in stress resilience. First, we confirmed that immunization with *M. vaccae* (0.1 mg s.c., in 100 µl borate-buffered saline on days -21, -14, and -7) increased hippocampal expression of IL-4 and IL-4-responsive genes, including CD200R1 in both male and female rats. To validate methods of blocking IL-4 signaling, we demonstrated that administration of the IL-4 blocker, soluble IL-4 receptor alpha (sIL-4ra; 5 µg, intra-cisterna magna [i.c.m.]) prevented the effects of co-administration of recombinant IL-4 (100 ng, i.c.m.) on hippocampal CD206 mRNA expression. Finally, to determine if blocking IL-4 signaling could prevent the effects of *M. vaccae* on hippocampal gene expression, we immunized adult male rats with *M. vaccae* or vehicle on days -21, -14, and -7, followed by i.c.m. injection of sIL-4ra or vehicle on day -1, and collected hippocampal tissue 24 h later. *M. vaccae* increased hippocampal IL-4, CD200R1, and CD206 mRNA expression, as expected. sIL-4ra had no effect on *M. vaccae*-induced increases in hippocampal IL-4 mRNA expression but prevented hippocampal CD200R1 and CD206 mRNA expression. Taken together, our results support the hypothesis that *M. vaccae* enhances immunoregulation in the CNS by increasing IL-4 and IL-4-dependent signaling, which might mitigate stress-induced neuroinflammatory and behavioral effects, thereby augmenting stress resilience.

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Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.01/U8

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Identifying the brain networks altered by gaming disorder defined by ICD-11: Cluster analysis by permutation test in calculating functional connectivity

Authors: *Y. OKAZAKI[1], S. KURIKI[2], H. KOBAYASHI[2], H. NAKAYAMA[3], S. MIHARA[3], S. HIGUCHI[3], A. ISHIYAMA[1];
[1]Waseda Univ., Shinjuku, Japan; [2]Tokyo Denki Univ., Tokyo, Japan; [3]Natl. Hosp. Organization Kurihama Med. and Addiction Ctr., Kanagawa, Japan

Abstract: We developed a new data-driven approach to estimate networks in the whole brain that were associated with Gaming Disorder (GD). There are many previous studies that have compared functional connectivity (FC) of healthy control (HC) and the population having disorders related to Internet-use and/or online-gaming. The FC is the correlation of time-series signals of resting state functional MR imaging (res-fMRI) between two brain regions. These papers have reported various brain regions having altered FC values in the disordered individuals. In this paper, in a FC analysis for the patients diagnosed with GD, we introduced Permutation Test (PMT) to control family wise error and estimated a cluster of brain areas which were linked to a core brain node having altered functional connectivity.
The experiment was conducted with the approval of the Ethics Committees of Kurihama Hospital, Tokyo Denki and Waseda Universities and with the informed consent of the subjects. We obtained res-fMRI data by using a 3T scanner for 30 HC participants and 26 GD patients. The patients were diagnosed with GD based on the 11th Revision of the International Classification of Diseases (ICD-11). We parcellated the whole brain into areas according to Automated Anatomical Labeling (AAL), excluding the cerebellum. We also divided the subjects into two subgroups, under 17 and over 18 years of age. We underwent a new approach for each of the two subgroups, as follows. We calculated FC values in all the connections of AAL areas and conducted Welch's t-test between HC and GD patients. Next, we identified pair-wise significant connections (or links) ($p<0.05$) with reduced FC (HC > GD), and increased (GD > HC). We performed PMTs in such a way that all subjects were randomly assigned into HC and GD groups and Welch's t-test was conducted. On each trial, we recorded the node with the largest cluster size and, after 5000 repetitions, obtained a histogram that showed the relation between the maximum cluster size and the frequency of its occurrence. The larger the cluster size was, the smaller frequency was. We found a cluster-level significant size ($p < 0.05$) from the histogram and selected the cluster of node-links whose size was larger than the critical size. From the result, we found core nodes of the links having reduced FC value in the frontal region and the occipital/parietal region for the GD group under 17 years, and the hippocampus and paracentral areas for the GD group over 18 years. These core nodes mainly linked to the cortical areas. Thus, we found obvious distinction of the core node areas between the young- and elder-age subgroups. Significant clusters of links having increased FC value in the GD patients were not found.

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Poster

501. Functional Brain Imaging and Multimodal Imaging

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Program #/Poster #: 501.02/U9

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Department of Biotechnology, Govt. of India Grant #BT/PR7180/MED/30/907/2012
NBRC core funds

Title: Somatosensory area 3b network is a composite of multiple distinct networks in macaque monkeys and humans

Authors: *J. THOMAS, D. SHERON, S. MOHANTA, N. JAIN;
NBRC, Manesar, India

Abstract: In the primary somatosensory cortex (area 3b) different somatotopic representations have different anatomical connectivity reflecting differences in functions of the body parts. However, the resting state functional network of the somatosensory cortex is traditionally taken to be a single network considering the entire area 3b as a single entity. We hypothesized that different somatotopic representations in area 3b will have different functional networks reflecting differences in their functions and the anatomical connectivity. Here we determined resting-state functional connectivity of the entire area 3b and its three sub-regions in two primate species - macaque monkeys and humans. We divided area 3b into three somatotopic regions - face (face 3b), hand (hand 3b) and rest of the medially represented body parts (med 3b). MRI scans of anesthetized macaque monkeys (n=5) and awake humans (n=23) were acquired using a 3T magnet (Philips Achieva). Studies were approved by institutional animal and human ethics committees. Data was analyzed using SPM8 following standard pre-processing steps which included slice-time correction, motion correction, co-registration, and smoothing. Functional MRI images were further processed and seed-based region-to-region and region-to-brain correlation analyses were performed using *CONN*. The regions of interest (ROIs) were drawn on subject-specific high-resolution MRI brain images for macaque monkeys and the standard MNI space for humans based on anatomical atlases, published data, and our fMRI scans and the electrophysiology mapping data. Data revealed that in both humans and monkeys, face 3b had higher overall connectivity than hand 3b and med 3b. Face 3b also had stronger connectivity with areas secondary somatosensory cortex (S2) and pre-motor ventral (PMv). In both the primate species, face 3b and med 3b showed homotopic bilateral connectivity while hand 3b had such bilateral connections only in humans. Strong connections between the three somatotopic ROIs were observed in humans but not in macaques. However, the connections of all the three topographic ROIs to adjacent representations in area 4 were stronger than intra-areal area 3b

connections. Our results show that different topographic representations have specific and distinct networks. The differences in the connectivity likely reflect differences in the functional usage of different body parts and its underlying anatomical connectivity. Results also suggest that considering the entire somatosensory area as a single unit in functional connectivity analysis will likely not reveal the complexity of the functional networks.

Disclosures: **J. Thomas:** None. **D. Sheron:** None. **S. Mohanta:** None. **N. Jain:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.03/U10

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Canadian Institutes of Health Research FRN 148365
Canadian Institutes of Health Research FRN 353372
Canada First Research Excellence Fund to BrainsCAN

Title: Effects of isoflurane anesthesia on functional networks in marmosets: Comparison to fully awake resting state functional magnetic resonance imaging

Authors: *Y. HORI, D. J. SCHAEFFER, K. M. GILBERT, L. K. HAYRYNEN, J. C. CLÉRY, J. S. GATI, R. S. MENON, S. EVERLING;
The Univ. of Western Ontario, London, ON, Canada

Abstract: The common marmoset (*Callithrix jacchus*), a New World Primate, is becoming increasingly popular as a non-human primate model for human brain function and dysfunction. To identify the functional network in marmoset, resting state functional MRI (RS-fMRI) is often used under anesthesia, despite clear evidence that anesthetics affect brain activation, in particular of the thalamus. However, it remains unclear how anesthetic agents affect functional network (FC) in marmosets. Here, we investigated the effects of isoflurane on FC by comparing RS-fMRI under a fully awake state with that under 1.5% isoflurane anesthesia. We had two primary objectives: The first was to elucidate the global changes of functional networks caused by anesthesia in marmosets. The second was to assess which thalamic FC is altered by anesthetics. Three marmosets were used in this study. To quantitatively compare the resting-state functional networks between awake and anesthetized groups, we used a dual regression technique that allows for voxel-wise comparisons of resting-state functional maps. To identify the strength of FC from left and right thalamus, the time courses from left and right thalamus were extracted for each scan and correlation maps (z-score maps) between thalamus and every other voxel in the brain were calculated. Here, the strength of FC was defined as the z-value. Our main results showed that: (1) isoflurane globally decreased FC in resting-state networks, but the structure of

the networks was preserved except for the default mode network; (2) isoflurane altered frontal-thalamic, cerebellar-thalamic and interhemispheric thalamic FC (Fig. 1). These findings bridge the gap between resting-state FC studies under anesthesia and awake conditions and provide insights into the effects of isoflurane on functional brain networks in primates.

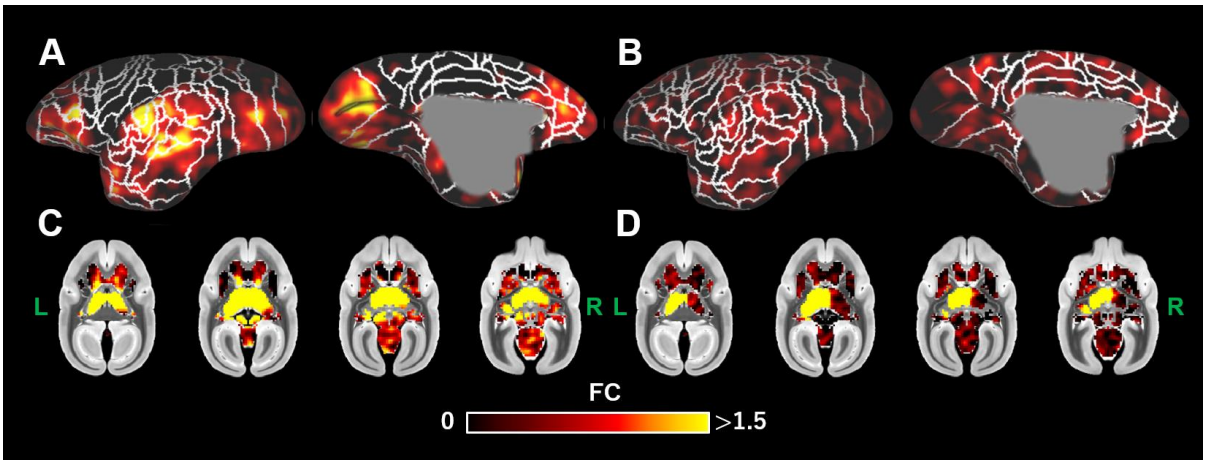


Fig. 1 Seed-based FCs from left thalamus for awake (A, C) and anesthetized marmosets (B, D).

Disclosures: **Y. Hori:** None. **D.J. Schaeffer:** None. **K.M. Gilbert:** None. **L.K. Hayrynen:** None. **J.C. Cléry:** None. **J.S. Gati:** None. **R.S. Menon:** None. **S. Everling:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.04/U11

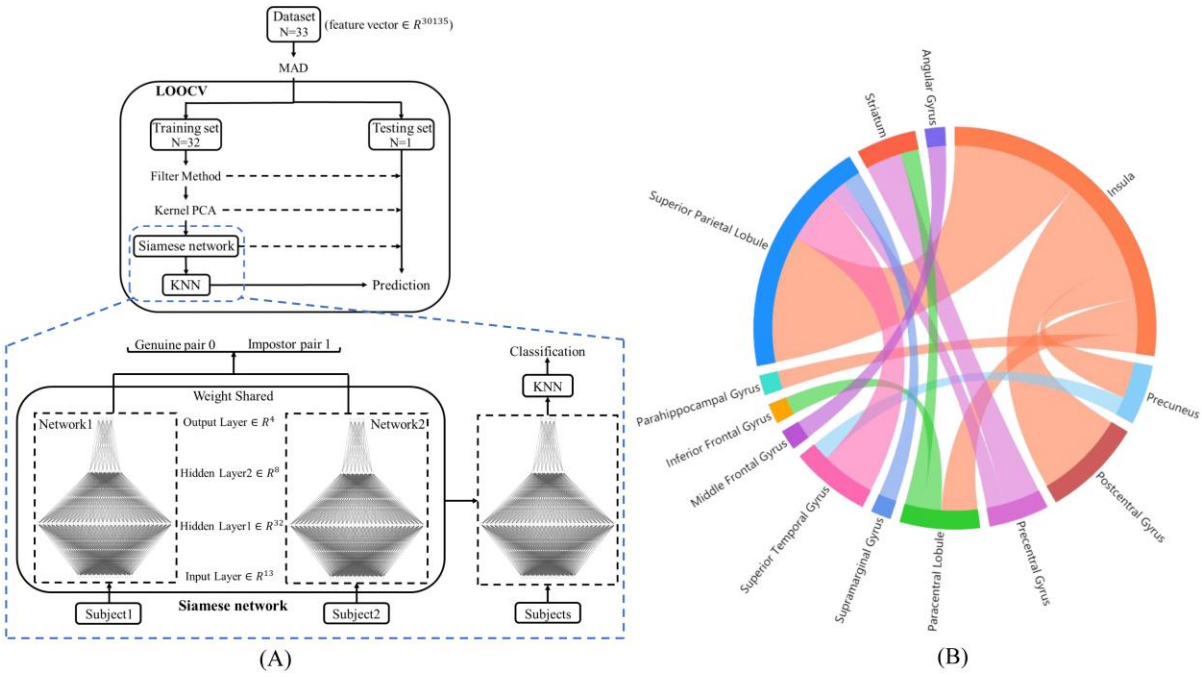
Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: National Natural Science Foundation of China under Grant Nos. 61431013, 81470816, 81501543, and 81730016
National Natural Science Foundation of Shaanxi Province under Grant No.2018JM3007
National Clinical Research Center for Digestive Diseases, Xi'an, China under Grant No. 2015BAI13B07
Intramural Research Program of the United States National Institute on Alcoholism and Alcohol Abuse, Z01AA3009

Title: Baseline functional connectivity predicts successful weight loss at six months after bariatric surgery

Authors: *W. ZHANG[1], G. LI[1], Y. HU[1], L. LIU[1], Y. WANG[1], Y. DING[1], C. HU[1], J. LI[1], G. JI[2], P. MANZA[3], G.-J. WANG[3], Y. ZHANG[1];
[1]Sch. of Life Sci. and Technology, Xidian Univ., Xi'an, China; [2]Natl. Clin. Res. Ctr. for Digestive Dis. and Xijing Hosp. of Digestive Diseases, Fourth Military Med. Univ., Xi'an, China; [3]Lab. of Neuroimaging, Natl. Inst. on Alcohol Abuse and Alcoholism, Bethesda, MD

Abstract: Laparoscopic-sleeve-gastrectomy (LSG) is one of the most effective treatments for obesity, and neuroimaging studies have shown LSG-induced brain functional and structural alterations in regions involved in food-intake control, cognitive-control and learning/memory. However, LSG's long-term therapeutic effects are varied among individuals with obesity. Therefore, we investigated whether pre-LSG brain resting-state functional connectivity (RSFC) could predict successful weight loss at six months post-LSG, using fMRI in 33 patients with obesity. Based on average percentage excess weight loss at six months, we performed a median split to divide participants into high and low weight-loss groups. First, functional MRI volumes were divided into 246 regions of interests (ROI) based on the Brainnetome Atlas and each subject had an 30135-feature vector RSFC vector (i.e., the bottom triangle of a 246 x 246 region connectivity matrix). Then, median absolute deviation (MAD), filter method (mutual information) and linear kernel principal component analysis (Kernel PCA) were used to eliminate redundant features and reduce the dimension of the feature set (**Fig 1A**). Next, 13 principal components (PCs) accounting for 60% of the variance were fed into the Siamese network and K-Nearest Neighbors (K-NN) classifier, which were trained and tested using leave-one-out cross validation (**Fig 1A**). This model was successful at predicting degree of weight loss: average accuracy = 84.85% and area under the curve = 0.85. The RSFCs located in the top fifth percentile of the RSFC weight distribution across each iteration were selected as the dominant RSFCs in each PC. The top PC (representing ~13% of the variance) was associated with a network that was dominated by brain regions involving insula, superior parietal lobule, striatum, pre- and postcentral gyrus, precuneus (**Fig 1B**). These findings reveal that brain functional connectivity can be used to predict successful weight-loss after bariatric surgery, and provide neurobiological insight into the heterogeneous outcomes associated with LSG.



Disclosures: **W. Zhang:** None. **G. Li:** None. **Y. Hu:** None. **L. Liu:** None. **Y. Wang:** None. **Y. Ding:** None. **C. Hu:** None. **J. Li:** None. **G. Ji:** None. **P. Manza:** None. **G. Wang:** None. **Y. Zhang:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.05/U12

Topic: I.08. Methods to Modulate Neural Activity

Support: APIN 2017-2018, Kellogg Company México S. de R. L. de C. V. INSK

Title: Metric alterations of brain connectivity in patients with morbid obesity undergoing gastric bypass

Authors: A. DELGADILLO-RAMÍREZ[1], ***P. VIEYRA-REYES**[1], P. FLORES-OCAMPO[1], L. PACHECO-BLAS[2], E. TRUJILLO-CONDES[1], G. MONTES DE OCA-LEMUS[1], C. JIMÉNEZ-GARCÉS[1], M. HERNÁNDEZ-GONZÁLEZ[1];
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Abstract: Modern studies argue that factors such as obesity lead to alterations in brain connectivity. Bariatric surgery is currently an available treatment that consistently maintains substantial weight loss, however, it is unknown if gastric bypass is a factor that leads to normal brain connectivity.
To analyze the above, functional magnetic resonance scans were obtained in the resting state (rs-FMRI) in 27 women with morbid obesity (body mass index of 40.4095±4.5 Kg/and body weight of 104.381±15.06 Kg) using a magnetic resonator GE 3.0 Teslas Discovery MR 750 ® with multiband gradient sequences. Data were collected in a longitudinal study one week before undergoing gastric bypass surgery and six months later.
A total brain functional connectivity matrix was constructed with normalized correlation coefficients using wavelet decomposition scales between regional signals dependent on BOLD blood oxygenation level and its coregistration in the JD Power atlas of 264 brain regions. The properties of the network were calculated in connectivity matrices with a connection density of 10-50%. Permutation tests were performed to evaluate the group differences ($p < 0.05$) for each network metric and each density.
The rs-FMRI data obtained pre-surgery showed an increase in the characteristic path length and a decrease in the weighted overall efficiency compared to their corresponding to six months, where an increase in the grouping coefficient, modularity, asortativity and strength for different densities was observed. However, these differences were not statistically significant.
The results obtained are consistent with studies comparing people with obesity *vs*. normal weight. The values obtained from the networks show that after gastric bypass, connectivity tends to that shown in normal weight subjects.
Funding source: APIN 2017-2018, Kellogg Company México S. de R. L. de C. V.

Disclosures: A. Delgadillo-Ramírez: None. **P. Vieyra-Reyes:** None. **P. Flores-Ocampo:** None. **L. Pacheco-Blas:** None. **E. Trujillo-Condes:** None. **G. Montes de Oca-Lemus:** None. **C. Jiménez-Garcés:** None. **M. Hernández-González:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.06/U13

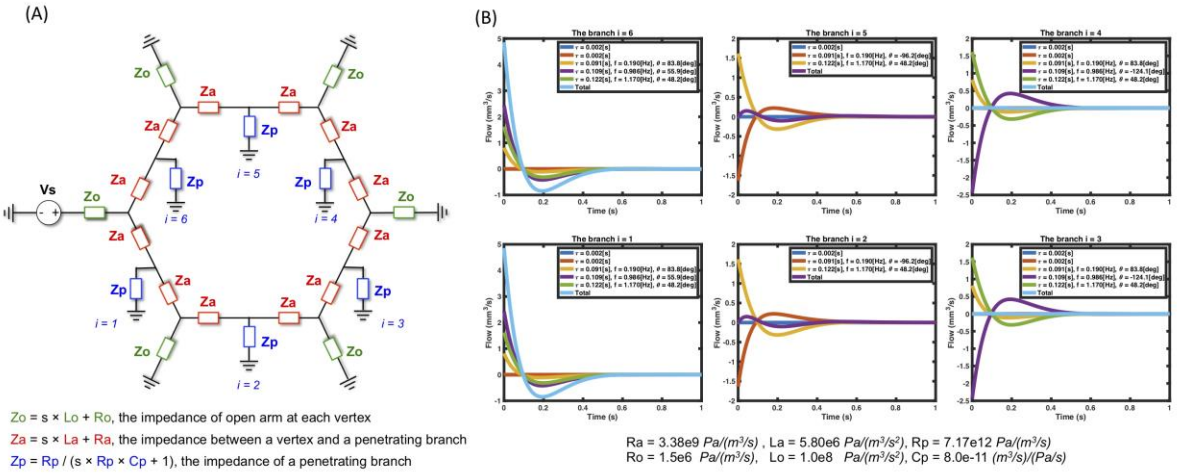
Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant NS095933

Title: Modeling the pial network: Linear hexagonal network that includes realistic vascular parameters

Authors: *X. ZOU, J. KIM, D. RESS;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Introduction: The human brain has a highly interconnected pial network to distribute blood from the large cerebral arteries to the penetrating arterioles and capillaries and eventually to veins. Accurate understanding of vascular functions is important to understand popular brain imaging methods that rely on the hemodynamic response function (HRF) to brief neural activation. The HRF typically has a positive peak at ~6 s and a form of underdamped oscillation with frequency f ~0.1 Hz and damping time tau ~3 s. Most neurovascular coupling models do not accurately portray the vascular topology and morphometry. It remains unclear how brief neural activation can provoke sluggish underdamped HRF through microscopic brain vessels. Here we present a linear lumped model based on the hexagonal idealization of the pial network. We postulate that the network has poles and zeros that create the observed HRF.
Methods: In our model (Fig. A), pial arteries form the edges of a hexagonal grid, and each edge has a branch at its center representing a penetrating arteriole and associated capillaries and venous drainage. An open arm originating at each vertex connects the grid to other pial arteries. The dynamic analogy of blood flow in a pial artery is that this rigid-pipe segment has a resistance and an inertance as functions of the blood density, the blood kinetic viscosity, the arterial radius, and the arterial length. Each penetrating branch is represented by a resistance and a parallel compliance because that penetrating arterioles and capillaries have very small radius and that downstream veins have compliant walls. We estimated the Ra, La, and Rp based on literature values of the human vascular dimensions and simulated the system response over a range of Ro, Lo, and Cp.
Results: An exemplary simulation of flow responses in each branch is shown in Fig. B.
Conclusions: Our results confirm that the hexagonal network can create underdamped HRF with f ~0.1 Hz. The flow response depends on the topological distance. The simulated tau is shorter than observed, suggesting that multiple hexagonal grids must be engaged.



Disclosures: X. Zou: None. **J. Kim:** None. **D. Ress:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.07/U14

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: ERC, DISCONN, #802371, to A.G.
NARSAD Independent Investigator Grant to A.G., #25861

Title: Silenced but still connected: Chemogenetic inactivation of the prefrontal cortex results in brain-wide fMRI hyper-synchronization

Authors: *C. CANELLA[1,2], F. ROCCHI[1,2], D. GUTIERREZ BARRAGAN[1], M. PASQUALETTI[1,3], A. GOZZI[1];
[1]Functional Neuroimaging Laboratory, Ctr. for Neurosci. and Cognitive Systems, Inst. Italiano di Tecnologia, Rovereto, Italy; [2]CIMeC Doctoral Sch. in Cognitive and Brain Sci., Univ. of Trento, Rovereto, Italy; [3]Dept. of Biology, Unit of Cell and Developmental Biol., Univ. of Pisa, Pisa, Italy

Abstract: Resting-state brain functional networks are characterized by regions exhibiting high connectivity density and centrality, for fast integration of neural processing. Consistent with a prominent role of these brain regions as “connectivity hubs”, it has been recently shown that their anatomical location is evolutionary conserved in primates and rodents (Liska et al., 2015), and encompasses higher-order polymodal neocortical areas, such as the medial prefrontal cortex (PFC). Importantly, the high level of centrality of functional connectivity hubs render them possible points of vulnerability for the integrity of brain networks, susceptible to disconnection and dysfunction in developmental and psychiatric disorders. According to this view, functional interference of connectivity hub regions would lead to brain-wide network de-synchronization. However, empirical confirmations of this hypothesis in the living brain are lacking. Here we used chemogenetic-fMRI (“chemo-fMRI”, Giorgi et al., 2017) to causally probe a role functional connectivity hubs as key stabilizers, and points of network vulnerability, in the mouse brain. Specifically, we used DREADD chemogenetics to obtain a sustained pan-neuronal silencing of the mouse anterior cingulate cortex, a core component of the mouse default-mode network, and a brain region exhibiting hub-like properties in the mouse and in primates (Liska et al., 2015). To inhibit this region, we bilaterally injected a recombinant adenovirus expressing the inhibitory DREADD receptrs hM4Di (or GFP) in the PFC of adult male C57BL6 mice (hM4Di group n=40, control group=40). Brain-wide network connectivity was mapped by using resting-state fMRI (rsfMRI) as previously described (Sforazzini et al., 2014) during chemogenetic silencing of the PFC, obtained upon an intravenous injection of CNO, or clozapine. The employed approach permits to remotely silence neuronal activity, with the aim to induce targeted and

reversible “virtual lesions” during resting-state fMRI acquisitions. We expected hub manipulations to result in widespread network disruption. Surprisingly, we found that chemogenetic silencing of the mouse PFC results in a paradoxical rsfMRI hyper-synchronization (i.e. functional over- connectivity) of the mouse default mode network, an effect that appeared to be relayed to other neocortical areas by thalamic nuclei. This effect was found to be associated with a dramatic reconfiguration of rsfMRI network coupling. Our results challenge the prevailing interpretation of functional connectivity alterations and network hub dysfunction in brain disorders.

Disclosures: **C. Canella:** None. **F. Rocchi:** None. **D. Gutierrez Barragan:** None. **M. Pasqualetti:** None. **A. Gozzi:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.08/U15

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

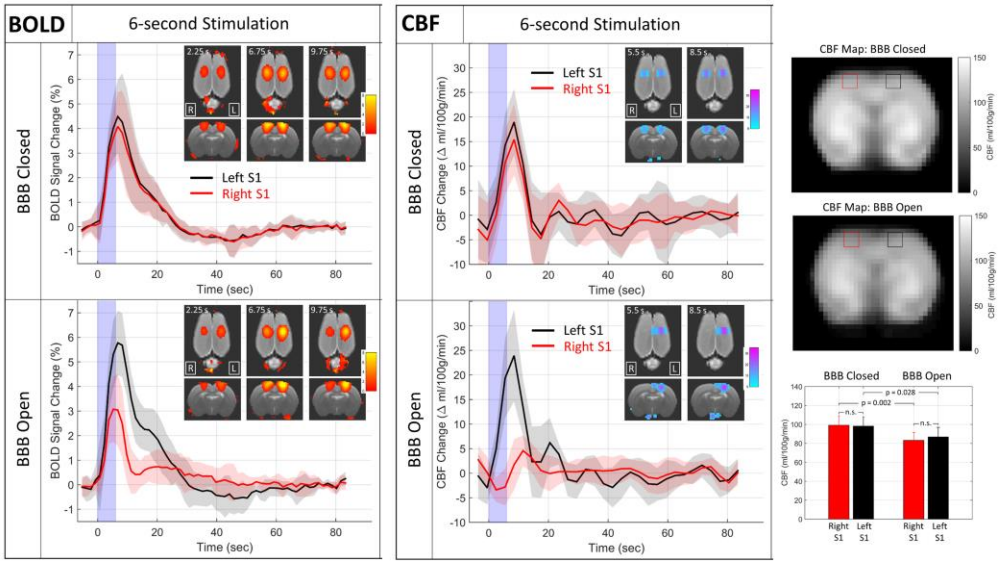
Support: K01EB023983
P01CA17464501

Title: The neurovascular response is attenuated by focused ultrasound-mediated disruption of the blood-brain barrier

Authors: ***N. TODD**[1], Y. ZHANG[1], M. S. LIVINGSTONE[2], D. BORSOOK[3], N. MCDANNOLD[1];
[1]Brigham and Women's Hosp., Boston, MA; [2]Harvard Med. Sch., Boston, MA; [3]PAIN Res. Group, Boston Children's Hosp., Boston, MA

Abstract: Focused ultrasound (FUS) with microbubbles can transiently open the blood brain barrier (BBB) for targeted delivery of pharmaceuticals into the brain. This method of BBB permeablization also leads to several secondary effects on the immune response, neuronal function and vascular hemodynamics. In this study, we use functional MRI to characterize the effects that FUS-BBB opening has on the neurovascular response to external stimuli in the rat brain. N=9 Sprague Dawley rats underwent separate MR imaging sessions with and without FUS-BBB opening. Functional MRI data was acquired using two different imaging sequences: blood-oxygen level dependent (BOLD) imaging captured the hemodynamic response associated with standard fMRI and arterial spin labeling (ASL) imaging was used to isolate cerebral blood flow (CBF) in particular. BBB disruption was targeted to the right somatosensory cortex in one hemisphere only. Bilateral hind paw electrical stimulation was used to activate the somatosensory cortex in both hemispheres at short (6 s) and long (18 s) stimulus durations. FUS-

BBB opening leads to a marked decrease in the changes in the BOLD response due to stimulation. There was no difference in baseline blood flow between the targeted hemisphere and the non-targeted hemisphere. However, changes in blood flow due to stimulation were almost completely suppressed in the targeted hemisphere. Results from the 6-second stimulation and baseline flow measurements are shown in Figure 1. It appears that FUS-BBB opening, at this low power level and one hour after sonication, affects either the signaling mechanism from the neurons to the vessels that is supposed to initiate increased blood flow to the active region or the ability of the vessels to respond to this signal.



Disclosures: **N. Todd:** None. **Y. Zhang:** None. **M.S. Livingstone:** None. **D. Borsook:** None. **N. McDannold:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.09/U16

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NMSS Grant RG150704951
NIH Grant R01AG 029523

Title: Cerebellar connectivity changes related to cognition in multiple sclerosis

Authors: ***M. D. ZUPPICHINI**[1], K. WEST[2], D. SIVAKOLUNDU[4], D. OKUDA[5], B. P. RYPMA[3];
[1]Behavioral and Brain Sci., Univ. of Texas At Dallas, Richardson, TX; [2]Ctr. for BrainHealth,

[3]Behavioral & Brain Sci., Univ. of Texas At Dallas, Dallas, TX; [4]Dept. of Biol. Sci., Univ. of Texas at Dallas, Dallas, TX; [5]Univ. of Texas at Southwestern, Dallas, TX

Abstract: Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease that includes processing speed-related cognitive impairments, the neural basis of which remains unknown. Recent research has suggested that cerebellum dysfunction plays a role in MS-related processing speed impairment. Due to extensive cortico-cerebellar connectivity, and the demyelinating nature of the MS disease course, we hypothesize that MS alters the connectivity between the cerebellum and cortical areas associated with cognitive abilities. MS and healthy control (HC) participants were scanned using a 3T MRI scanner with an echo-planar imaging scan during rest. All preprocessing and analyses were performed using Analysis of Functional NeuroImages. Average timeseries were created for each participants' cerebellum region of interest (cROI) and a Pearson's correlation coefficient was computed between the cROI and all cortical voxels. Correlation coefficients were then transformed to z-scores for between-group comparison. Results from the independent-samples t-test showed that MS had significantly lower z-scores in cuneus and cingulate gyrus. The results suggest MS-related reductions in cortico-cerebellar connectivity. MS alters connectivity between the cerebellum and cortical areas within the default-mode and executive control networks that are associated with cognitive impairments.

Disclosures: M.D. Zuppichini: None. **K. West:** None. **D. Sivakolundu:** None. **B.P. Rypma:** None. **D. Okuda:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Biogen. F. Consulting Fees (e.g., advisory boards); Acorda, Genzyme, TEVA Neuroscience, EMD Serono, Genentech.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.10/U17

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Prediction of individual cognitive ability using resting-state functional connectivity

Authors: *E. DHAMALA[1], K. JAMISON[2], S. DENNIS[3], A. KUCEYESKI[2];
[1]Neurosci., [2]Radiology, Weill Cornell Med., New York, NY; [3]Sarah Lawrence Col., New York, NY

Abstract: Resting-state functional connectivity (rsFC) measures temporal correlation of spontaneous blood-oxygen-level dependent (BOLD) signal among spatially distributed brain regions. Intrinsic functional connectivity has been shown to reflect performance variability in several cognitive domains in healthy individuals (Seeley, WW. *et al.*, 2007; van den Heuvel, MP. *et al.*, 2009). A recent study used rsFC to predict 58 different behavioural measures with

prediction accuracies ranging from 0 to 0.45 (Li, J. *et al.*, 2019). Thus, rsFC may hold promise to reveal functional biomarkers underlying cognitive abilities. Using publicly available data from the Human Connectome Project, we examined resting state BOLD time series data from 1003 subjects (469 males; ages 22-35). Zero-lag Pearson correlation with regression of the global signal and its temporal derivative were used to generate a rsFC matrix for each subject using an 86 region FreeSurfer atlas (34 cortical areas and 9 subcortical areas per hemisphere). Each subject's rsFC matrix was Fisher's z-score transformed. Cognitive measures used in this study were the fluid cognition composite, crystallized cognition composite, and total cognitive function composite, all of which are based on an individual's performance on different NIH Toolbox tests. The data were separated into training (90%) and testing (10%) subsets. Linear ridge regression with leave-one-out cross validation and grid search were used to optimize the regularization strength hyperparameter. We were able to predict an individual's cognitive score using their rsFC with a coefficient of determination (R^2) of 0.12, 0.10, and 0.19 for fluid, crystallized, and total cognition composites, respectively, with corresponding Pearson correlation values of 0.38. 0.42, and 0.46. Overall, rsFC accounted for 12.0%, 16.3%, and 21.2% of the explained variance score for fluid, crystallized, and total cognition composites, respectively. For each of the three models, we found that cortico-cortical functional connectivity was most important for the prediction.

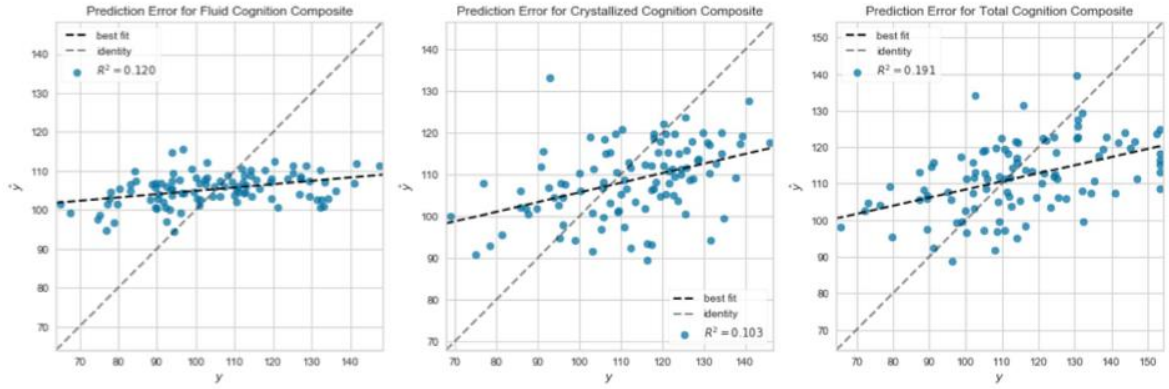


Fig. 1: Prediction errors for fluid (left), crystallized (middle), and total (right) cognition composite. True values (y) are plotted on the x axis and predicted values (ŷ) on the y-axis. The coefficient of determination (R^2) for each prediction is shown on the graph. Pearson correlation between the true and predicted values are 0.38 (fluid), 0.42 (crystallized), and 0.46 (total). Resting-state functional connectivity accounted for 12.0% (fluid), 16.3% (crystallized) and 21.2% (total) of the explained variance.

Disclosures: **E. Dhamala:** None. **K. Jamison:** None. **S. Dennis:** None. **A. Kuceyeski:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.11/U18

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH BRAIN Initiative support

Title: An MRI compatible headstage for simultaneous electrophysiology and fMRI recording

Authors: *M. SORENSON[1], Y.-Y. I. SHIH[2], S.-H. LEE[2], R. FRANKLIN[1], M. GERHARDT[1], F. SOLZBACHER[3];
[1]Blackrock Microsystems, Salt Lake City, UT; [2]Univ. of North Carolina At Chapel Hill, Chapel Hill, NC; [3]Univ. of Utah, Salt Lake City, UT

Abstract: Motivation/problem statement:
Electrophysiology recordings from implanted electrodes while simultaneously performing MRI scans presents challenges. The MRI machine can induce noise into electrophysiology recordings. Likewise, electronics and/or cables inside the MRI can induce artifacts into the MRI images. Safety issues, based on material choices, are also a concern.
Methods/ approach:
We designed an MRI compatible headstage preamplifier capable of recording local field potentials (LFP) and single unit activity from a microelectrode array. The approach taken was to buffer the neural signals close to the electrode to reduce noise pickup from antenna effects and then transfer the buffered signal through a shielded cable to a recording system located outside of the MRI environment.
The headstage was bench tested to show comparable performance to non-MRI compatible headstages used for LFP and single unit recording. It was then tested in an MRI for signal quality during scans as well as for imaging artifacts. Finally, it was tested in conjunction with an MRI compatible electrode in a rat model to show efficacy.
Results:
Bench testing of the MR-compatible headstage showed similar quality to existing headstages in terms of noise and frequency response. Testing in the MRI showed minimal imaging artifacts in the area of interest at the electrodes and acceptable noise levels in the electrophysiology recordings. In-Vivo testing proved efficacy of the MRI compatible headstage.
Conclusion/implications:
The MRI compatible headstage designed provides simultaneous electrophysiology recording and fMRI imaging. This provides researchers with a new tool for their work.

Disclosures: **M. Sorenson:** A. Employment/Salary (full or part-time):; Blackrock Microsystems (full). **Y.I. Shih:** None. **S. Lee:** None. **R. Franklin:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. **M. Gerhardt:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. **F. Solzbacher:** A. Employment/Salary (full or part-time):; Blackrock Microsystems.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.12/U19

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: LANIREM
CONACYT (716272/634009)

Title: Hemodynamic correlates of posterior alpha rhythm during eyes-open and eyes-closed states: A simultaneous EEG-fMRI study

Authors: *J. E. GALLEGO RUDOLF[1], E. H. PASAYE-ALCARÁZ[1], M. CORSI-CABRERA[2];
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Abstract: Introduction: Simultaneous Electroencephalography and functional Magnetic Resonance Imaging recording (EEG-fMRI) is a multimodal neuroimaging tool that intends to assess the electrophysiological and hemodynamic correlates of brain activity. Despite efforts, data quality remains an important issue, especially for EEG. In this work, we compared different ballistocardiographic (BCG) artifact correction methods applied to EEG data collected during EEG-fMRI. We evaluated both artifact reduction and EEG signal preservation (focusing on posterior alpha rhythm). Next, we performed an EEG-informed fMRI analysis using EEG alpha power fluctuations as a BOLD signal predictor. Method: EEG was recorded from 20 healthy subjects outside the MR environment and during EEG-fMRI while they performed a simple eyes-closure, eyes-opening block-design task (EC-EO task). Gradient artifact (GA) was removed using artifact template subtraction (ATS). BCG artifact was corrected using either ATS, Optimal Basis Set (OBS), Independent Component Analysis (ICA) or the combination of OBS and ICA. Efficacy of artifact removal was assessed by comparing EEG power between the corrected EEG-fMRI and the outside data. Signal preservation was assessed by evaluating alpha power reactivity to the EC-EO task in the corrected signals. For EEG-informed fMRI analysis, ICA was used to extract alpha power fluctuations. Resulting time series were convolved with a hemodynamic response function and used as BOLD signal predictors in the subject-level analysis. Group analysis was performed using permutation-based inference. Results: Satisfactory GA cleaning can be performed using ATS approach. Although all methods reduce the BCG artifact, residuals remain. ICA feature extraction rescues posterior alpha activity from the contaminated signals. Back-reconstructed EEG signal shows a clear reactivity to the EC-EO task. Group analysis revealed an inverse relationship between alpha power fluctuations and BOLD signal in occipital and parietal cortices. EEG-informed fMRI derived results show great similarity to the results

obtained when using conventional task-design predictor inference. Conclusion: EEG alpha power fluctuations can be preserved after correcting the data obtained from simultaneous recordings and using feature extractions tools such as ICA. The inverse relation between EEG alpha power and BOLD signal in visual cortices is a consistently observed phenomenon in EEG-fMRI studies. These findings support EEG-informed fMRI analysis as a valuable tool that can be used to investigate the interactions between electrophysiological and hemodynamic responses in the human brain.

Disclosures: J.E. Gallego Rudolf: None. **E.H. Pasaye-Alcaráz:** None. **M. Corsi-Cabrera:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.13/U20

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Development of the functional ultrasound imaging platform for awake and behaving mice in preclinical drug discovery

Authors: *A. SHATILLO, H. VAHERTO, J. KOPONEN, D. MISZCZUK;
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Abstract: Anesthesia in preclinical functional neuroimaging is one of the major confounding factors, hindering the application of the technology for drug discovery and lowering the translational value of the obtained results. Substantial effects on the basic vital functions and physiology, interference with brain neurotransmitter systems and inhibition of the neuronal activity are the most common negatives.
Functional ultrasound (fUS) is a novel imaging technique that was recently introduced to the field of preclinical CNS research. Method utilizes latest technological advancements for ultrafast plane-wave acquisition of doppler ultrasound signal with real-time data processing. Applied to neuroimaging in laboratory animals, this approach enables high sensitivity functional measurement of relative cerebral blood volume (rCBV) changes with excellent spatio-temporal resolution. Combined with the imaging depth to cover the brain in coronal dimension in both rats and mice it makes a perfect platform for functional studies similar to fMRI in humans and animals. Moreover, non-invasive signal recording and small footprint of the fUS sensor creates a perfect opportunity for awake imaging in non-anesthetized animals with minimal stress and habituation period, making it much more cost-effective and feasible alternative to awake fMRI. In this methodological study we sought to setup a robustly working platform for awake fUS imaging in mice that can be routinely used for preclinical drug discovery in CNS.
fUS prototype device (Iconeus, Paris, France) and MobileHomeCage v5 (MHC, Neurotar,

Helsinki) with platform tracking were used for habituation and awake imaging purposes. Mice (C57bl/6J) were surgically implanted with MHC-compatible 3D-printed titanium alloy head plates positioned over the occipital bone. After one week of recovery, training protocol that consisted of 8 training sessions of increasing duration (5 to 45 min) was initiated, starting with basic handling on D1, fixation in MHC on D2-3 and mock imaging on D4. Actual data acquisition was performed on D5 and consisted of two 10 minutes-long resting state imaging sessions with 400 ms temporal resolution. Full power doppler time series from selected brain regions were split into 3-4 artifacts-free epochs, low-pass filtered for the correlation analysis and visualized by connectivity matrices.
Awake fUS imaging platform established and described within this study, demonstrates the utility and benefits of this cost-efficient methodology when applied to preclinical translational research and drug discovery as a powerful alternative to awake fMRI or imaging in anesthetized animals.

Disclosures: **A. Shatillo:** None. **H. Vaherto:** None. **J. Koponen:** None. **D. Miszczuk:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.14/U21

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Sir Henry Dale Fellowship, Wellcome Trust and the Royal Society 102584/Z/13/Z
Wellcome Centre for Integrative Neuroimaging, Wellcome Trust 203139/Z/16/Z

Title: 7t MRI: Combined fMRI-fMRS of m1 during rest and motor tasks, linking bold and neurochemicals

Authors: *J. M. LEVENSTEIN[1,2], W. CLARKE[1], B. IP[1], U. EMIR[3], P. BANDETTINI[2], C. J. STAGG[1];
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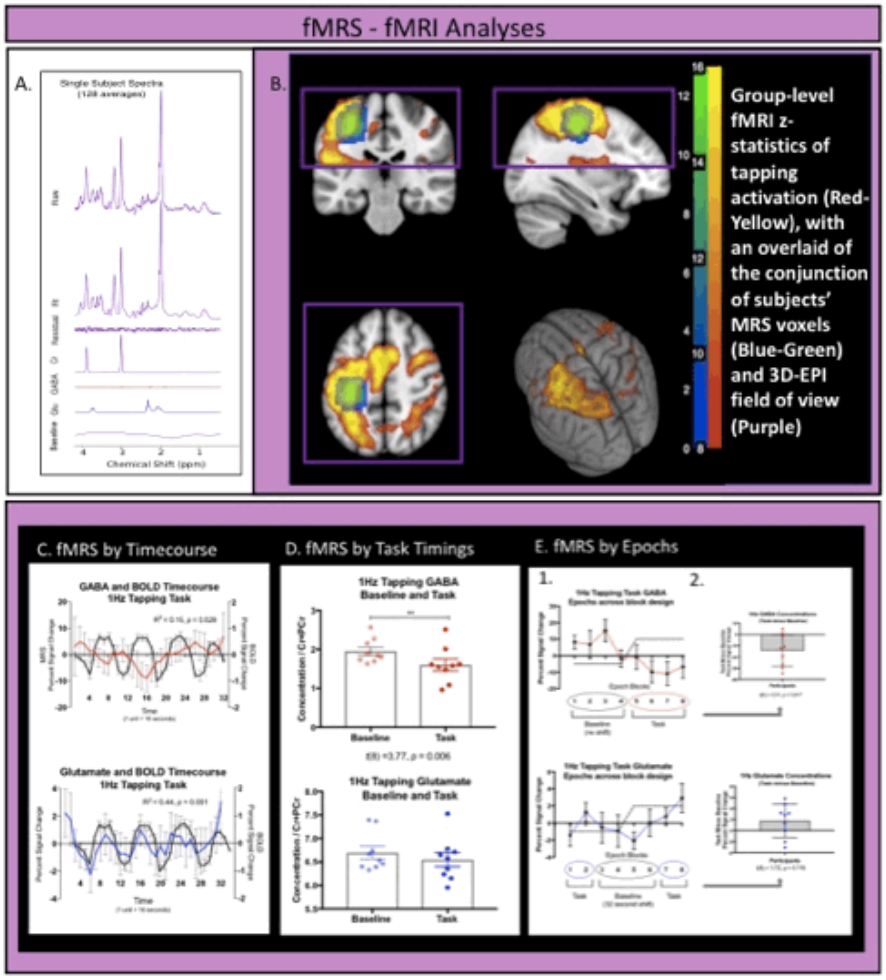
Abstract: Functional magnetic resonance spectroscopy (fMRS) is an in-vivo imaging technique that shows promise towards measuring task-relevant modulation of neurotransmitters in the human brain. To more fully understand the metabolism underlying brain function, this is the first study in the motor cortex to apply a novel MR sequence acquiring concurrent measures of BOLD and fMRS.
Twenty-four participants were recruited into study1 (n=12,6f) and study2 (n=12,6f). fMRS data

were analyzed with MRspa and LCmodel (fig1A). fMRI data were analyzed using FSL. In study1, participants performed a 1Hz block-design finger-tapping task. Fig.1B demonstrates significant task BOLD activity in the MRS voxel. The first fMRS analysis processes the data across-time (fig.1C). The second analysis applies the timings of the task to create baseline and task condition spectra (fig.1D). The final analysis generates time-locked epochs(fig.1E). Group-level correlations between task fMRS and BOLD timecourses demonstrate a significant negative correlation with GABA (R^2=0.15, p=0.028). Applying a 32 second shift to the BOLD timecourse results in a significant positive correlation with glutamate (R^2=0.44, p<0.001). Applying the task timings to generate condition specific spectra resulted in a significant GABA decrease during the 1Hz task (t(8)=3.77, p=0.006). Epochs of MRS spectra show decreasing GABA during tapping periods (fig.1F1), with significant decreases in task-minus-baseline (t(8) =3.01, p=0.017).

These results demonstrate a decrease in GABA concentration during 1Hz finger tapping compared to rest. Task-induced changes in glutamate positively correlate with the BOLD timecourses when a 32 second lag is applied, suggesting a potential task-induced neurochemical delay. While these preliminary findings still require further investigation, the results highlight the need for greater understanding of metabolism dynamics in the human brain, and their relation to BOLD imaging. Our forthcoming study2 results aim to address these needs.



Disclosures: **J.M. Levenstein:** None. **W. Clarke:** None. **B. Ip:** None. **U. Emir:** None. **P. Bandettini:** None. **C.J. Stagg:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.15/U22

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: BBSRC ICase
Welcome Trust Grant 101092/Z/13/Z

Title: Differential effects of the anaesthetic agents sevoflurane and isoflurane on functional connectivity in the rhesus macaque cortex

Authors: C. B. C. R. POULLIAS[1], K. L. MURPHY[2], *K. KRUG[1], J. SALLET[1];
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Abstract: The study of resting state connectivity detects temporal correlation in the spontaneous blood oxygen level-dependent (BOLD) signal for subjects at rest in an MRI scanner - a useful means of investigating the brain's functional organization and potential neurological alterations. Better behavioural control makes acquiring resting-state data in awake humans straightforward. This is more challenging for non-human primates like the Rhesus macaque - a major model of human brain function. Thus, many studies acquire resting state data in anaesthetized animals. However, different anaesthetic agents may have differential effects on brain physiology and thus functional connectivity. To investigate their impact, we compared directly functional connectivity with two commonly employed, volatile anaesthetic agents. We acquired two resting state MR datasets (EPI sequence; 800 or 1600 volumes) from 24 Rhesus macaques. The animals scanned under isoflurane or sevoflorane were matched for depth of anaesthesia (assessed by the min. alveolar concentration (MAC) value), age, delay between sedation and data collection, and physiological values (blood pressure, heart rate, exhaled CO2 concentration). The first group was anesthetized using sevoflurane (MAC value range: 0.78-1.3, 10 animals), the second using isoflurane (MAC value range: 0.61-1.23, 14 animals). We combined seed based analysis (SBCA) and individual component analysis (ICA, using the FSL function MELODIC with 30 individual components) to investigate the differential impact of isoflurane and sevoflurane on functional connectivity, especially on networks related to visual and decision processes. The results from both SBCA and MELODIC revealed higher z-score correlation values for sevoflurane than isoflurane. However, the functional maps obtained were less spatially selective under sevoflurane than isoflurane. Our results show that the two agents despite maintaining anaesthesia

at comparable depths differentially impact brain activity. Therefore the type of anaesthetic agent constitutes a key parameter for interpreting functional connectivity data.

Disclosures: C.B.C.R. Poullias: None. **K.L. Murphy:** None. **K. Krug:** None. **J. Sallet:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.16/U23

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Using multimodal MRI to investigate brain structure, function, and capillary density in a genetic model of diabetes

Authors: *C. LAWSON, K. RENTRUP, J. QIAO, X. CAI, P. KULKARNI, C. FERRIS; Psychology, Northeastern Univ. Dept. of Psychology, Boston, MA

Abstract: Type 2 Diabetes (T2D) is a serious metabolic disorder affecting 16 million people in the US, with prevalence expected to reach more than 54.9 million Americans by 2030. Small vessel disease is prominent in T2D as evidenced by the high incidence of retinopathy, nephropathy and gangrene. The present study used non-invasive multimodal magnetic resonance imaging (MRI) to characterize small vessel disease in the brain and the neuropathological features of late-stage diabetes using the transgenic BBZDR/Wor rat, an animal model of T2D provided by Biomere (Worcester, MA). Imaging was performed on BBZDR/Wor rats and their age-matched wild type controls using a 7.0T MRI scanner. The imaging modalities included T1 weighted voxel-based morphometry, diffusion weighted imaging with quantitative anisotropy, resting state BOLD functional connectivity, ferumoxytol contrast-enhanced imaging and finally quantitative ultrashort TE contrast enhanced MRI (QUTE-CE). This final imaging technique was particularly relevant as it allows visualization brain vasculature and cerebral blood volume using iron oxide nanoparticles to track blood throughout the brain. All images were registered to a 3D MRI Rat Atlas with 171 segmented and annotated brain areas used to generate an unbiased computational analysis of all data. Cognitive decline, alterations in hippocampal volume and reduced functional connectivity across multiple neural circuits are clinical features of T2D. As such, it was hypothesized that T2D rats would show similar problems in cognition and neuroradiological evidence of alterations in brain areas and neural circuits involved in learning and memory. Specifically, it was predicted that T2D rats would present with hypovascularity in the hippocampal complex and loss of vascular responsivity to carbon dioxide challenge as compared to age-matched. Both anatomical brain area scans and neural circuitry imaging revealed significant differences between the wild type and T2D rat brains throughout the cortex and areas of the hippocampus. The angiopathy associated with diabetes was consistent in the

central nervous system of the T2D rats, with decreased capillary density and microbleeds throughout the brains.

Disclosures: C. Lawson: None. **K. Rentrup:** None. **X. Cai:** None. **P. Kulkarni:** None. **C. Ferris:** Other; Craig Ferris has a financial interest in Animal Imaging Research the company that makes the rat imaging equipment.. **J. Qiao:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.17/U24

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: P41-EB015896
P41-EB015891
R00-MH111748
R01-EB019437
R01-MH111438
R01-MH111419
S10-RR023043

Title: Probing the potential biophysical mechanisms of fast fMRI signals

Authors: *J. E. CHEN[1], G. H. GLOVER[2], N. E. FULTZ[3], N. A. OHRINGER[3], B. R. ROSEN[4], J. R. POLIMENI[5], L. D. LEWIS[6];
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Abstract: fMRI studies have mostly focused on slow signals due to the presumed slow speed of the hemodynamic response, which was thought to limit neural signals to the <0.3 Hz range. However, recent resting state and task fMRI studies have detected neural fluctuations at frequencies of up to 0.75 Hz, well above the limits predicted by the canonical hemodynamic response function (HRF). The mechanisms of these fast fMRI signals are not known, limiting our analysis and interpretation of these signals. In this study, we examined two potential biophysical mechanisms that may underlie high-frequency fMRI signals. **Mechanism I: tasks with lower contrast levels elicit faster HRFs.** As resting-state neural activity likely comprises low intensity levels relative to task-driven responses, we asked whether low-intensity stimuli could reproduce the observed fast hemodynamic responses, which would in turn lead to high-frequency fMRI signals. Two sensory tasks with graded contrast levels were performed to test this hypothesis: (1)

8 subjects received a vibrotactile stimulation at three contrast levels; and (2) 10 subjects received visual stimulation with a checkerboard pattern flickering at two luminance contrasts. In both tasks, HRFs at lower contrast levels exhibited shorter time-to-peak and narrower full-width-of-half-maximum. Using simultaneous EEG, we found no salient distinctions in steady-state visual evoked potential amplitudes between different visual contrasts, suggesting these faster HRFs were due to altered hemodynamics. **Mechanism II: high spatial resolution can enhance the sensitivity of fMRI to high-frequency oscillations.** Smaller voxel sizes can reduce contamination from large veins that have slow responses, and mitigate phase cancellation among distinct HRFs within one voxel. Furthermore, as the voxel size decreases to the sub-millimeter regime, alternative, faster non-BOLD signals (e.g., inflow and dynamic partial volume effects) may become more evident, and classical hemodynamics may no longer apply. To test this hypothesis, we evaluated the inter-voxel variability of HRFs evoked by an event-related visual stimulus at very high spatial resolutions: 5 subjects at 3T (1.23X1.23X1.5 mm^3), and 5 subjects at 7T (0.8 mm^3 iso.). We observed notable variability across voxels, with the slowest HRFs being approximately twice long as the fastest ones; and a large number of voxels exhibiting much faster responses than the canonical HRF. Collectively, our results suggest that both low-intensity task contrasts and high spatial resolution can result in much faster HRFs than conventional models, supporting the potential of fast fMRI for mapping brain oscillations.

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Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.18/U25

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: (NIH) grant nos. 5P01AG052350 (B.V.Z.)
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Alzheimer's Association strategic 509279 grant and the Foundation Leducq reference no. 16 CVD 05
NIH grant nos. P50AG05681 (J.C.M.), P01AG03991 (J.C.M.), and P01AG026276 (J.C.M.)

Title: Effect of ApoE ε4 carriers on BBB permeability, Amyloid-b and Tau in cognitively normal subjects - A multimodal MRI/PET study

Authors: A. C. CHAKHOYAN[1], A. MONTAGNE[1], M. D. SWEENEY[1], D. A. NATION[1], J. PA[2], T. BENZINGER[4], J. C. MORRIS[5], H. C. CHUI[3], A. W. TOGA[2], B. V. ZLOKOVIC[1]; [1]Dept. of Physiol. and Neuroscience, Zilkha Neurogenetic Institute, Keck Sch. of Med., [2]Lab. of

Neuro Imaging, USC Stevens Neuroimaging and Informatics Inst., [3]Alzheimer's Dis. Res. Ctr., USC, Los Angeles, CA; [4]Mallinckrodt Inst. of Radiology, [5]Dept. of Neurol. and The Hope Ctr. for Neurodegenerative Disorders, Washington Univ. in St. Louis Sch. of Med., St. Louis, MO

Abstract: Purpose: Early blood-brain barrier (BBB) breakdown is an early biomarker of human cognitive dysfunction independent of Amyloid-β and Tau. ApoE4 is a major genetic risk factor for Alzheimer's disease. Here, we determined cross-sectionally the effect of ApoE4 gene on vessel permeability, and Amyloid-β and Tau biomarkers in cognitively normal patients by using advanced imaging techniques - MRI and PET.
Methods: Sixty-one subjects were included in this study. Out of 61 subjects, 37 were ApoE4 non-carriers (3/3) and 24 ApoE4 carriers (3/4+4/4). In ApoE4 non-carriers and carriers, 70.2% and 66.2 were female with no difference in age (median: 68 vs. 67 years) and years of education (median: 17.5 vs. 17.3 years), respectively. Amyloid-β and Tau PET images were first converted to standardized uptake value (SUV) then normalized by whole cerebellum (SUVR). DCE-MRI was used to extract volume transfer constant (Ktrans) which reflects the influx rate of gadolinium contrast from blood plasma into the brain tissue extravascular space. The medio-temporal (MTL) lobe was considered as a principal region of interest segmented on high resolution 3D-T1w images.
Results: Results suggest that Amyloid-β and Tau were not significantly different in MTL region between ApoE4 non-carriers and carriers. Interestingly, only Ktrans values were significantly higher in ApoE4 carriers. Linear regression analyses revealed no correlation between Ktrans values, Amyloid-β and Tau SUVR.
Conclusions: Multimodal MRI/PET demonstrate BBB breakdown in cognitively normal ApoE4 carriers compared to non-carriers that is not affected by Amyloid-β and Tau.

Disclosures: A.C. Chakhoyan: None. **A. Montagne:** None. **M.D. Sweeney:** None. **D.A. Nation:** None. **J. Pa:** None. **T. Benzinger:** None. **J.C. Morris:** None. **H.C. Chui:** None. **A.W. Toga:** None. **B.V. Zlokovic:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.19/U26

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Loneliness is associated with altered regional cerebral blood flow: An arterial spin labeling imaging study

Authors: *Y.-W. CHEN[1], T. CANLI[2];
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Abstract: Perceived social isolation, commonly referred to as loneliness, is defined as the subjective feeling that one's social needs are not satisfied by both quantity and quality of one's social relationships. Loneliness has been linked to a broad range of adverse physical and mental health consequences. Thus, there is an interest in identifying the neural regions and underlying molecular processes by which subjective social isolation adversely affects health. Prior imaging studies reported that high levels of loneliness were associated with increased activation to unpleasant social stimuli in the visual cortex, and with decreased activation to pleasant social stimuli in the ventral striatum. Another study reported an increased functional connectivity density cluster that was centered over the lingual gyrus. Whereas prior study results were based on indirect measures of neural activation (i.e., blood-oxygenation-level-dependent imaging), the current study was based on direct measures of regional cerebral blood flow (rCBF) using resting-state Pulsed Arterial Spin Labeling (PASL) imaging, which is thought to be highly correlated with cerebral metabolism. Eight-two healthy young adults (M = 21.51, SD = 4.64, 49 females) were included in our current study. We examined the association between individual perceived loneliness (Revised UCLA Loneliness Scale, M = 42.29, SD = 10.01) and resting-state rCBF. Whole-brain regression analyses (uncorrected $p < .005$, extend 50 voxels) revealed negative associations between loneliness and left-lateralized rCBF in the insula, postcentral gyrus, lingual, middle occipital, and parahippocampal gyri. These results replicate and further extend prior work implicating a widespread network of regions involved in somatosensory, visual and affective-cognitive processing.

Disclosures: **Y. Chen:** None. **T. Canli:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.20/U27

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

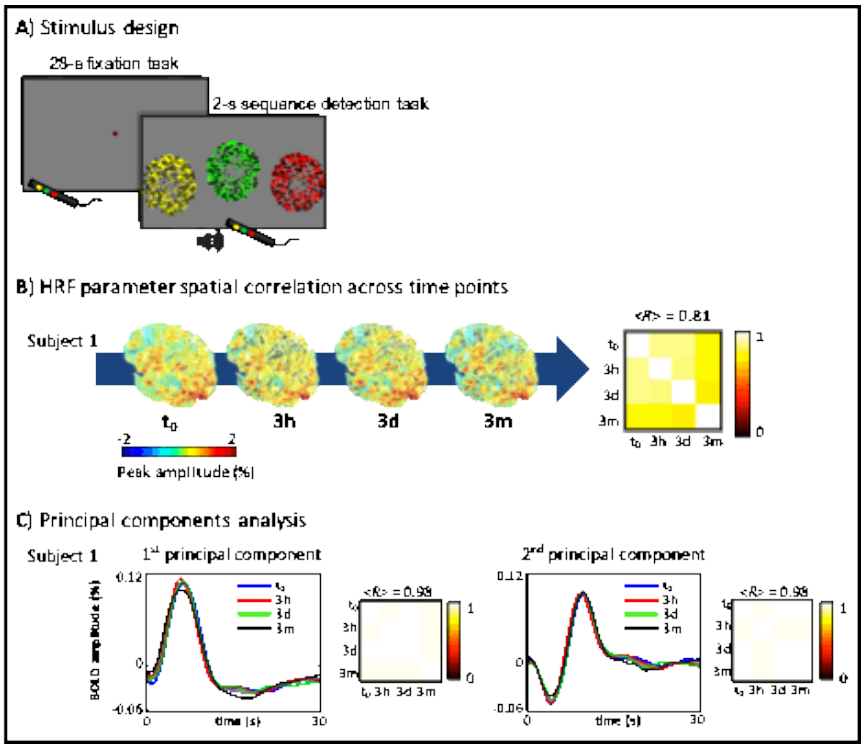
Support: NIH Grant R01NS095933
NIH Grant R21HL108143
NSF Grant BCS1063774

Title: Temporal stability of the hemodynamic response function in human cortex

Authors: *A. TAYLOR, X. ZOU, J. KIM, D. RESS;
Baylor Col. of Med., Houston, TX

Abstract: Introduction: We recently found that a brief stimulus with speeded task will evoke the hemodynamic response function (HRF) across most of cortex. Here, we measure HRFs within healthy subjects over the course of four sessions separated by intervals of three hours, three days,

and three months to quantify HRF variations over time.**Methods:**Subjects (*N*=8) performed an audiovisual sequence detection task for 2 seconds (Fig A). The visual stimulation consisted of three circular regions of randomly flickering colored dots with a corresponding audio stimulus of bandpass-filtered white noise. 80 HRFs were collected per session. Imaging was performed on a 3T Siemens Trio scanner with a 32-channel head coil. FMRI data were collected using SMS-accelerated EPI (2-mm voxels; TR = 1.25 s; 57 slices; whole-cortex Rx). These data were registered to anatomical images (0.7-mm MP-RAGE) that was segmented using FreeSurfer to delineate cortical gray matter. HRF time series data from central gray matter layers were parameterized for each voxel. **Results:**Surface maps (Fig B) of HRF parameters show highly correlated spatial patterns across the four time points for activation (R= 0.73±0.15) and peak amplitude (R= 0.68±0.18). Temporal parameters, TTP (R = 0.20±0.08) and FWHM (R = 0.17±0.06), are much less spatially correlated. Principal component analysis (Fig C) of the HRF time series across voxels show strong correlations (PC1: R= 0.96; PC2: R= 0.93), suggesting stable temporal dynamics across time points. **Discussion:**Across a long time span, HRF amplitude parameters are strongly spatially correlated whereas the temporal parameters showed greater variation. However, principal component analysis suggest that temporal dynamics are reasonably consistent across time within each subject. More detailed voxel-by-voxel analysis of the temporal dynamics is in progress. Our observations are inconsistent with fMRI studies at coarser resolutions that showed significant variations across sessions, suggesting that the HRF is more stable within cortical gray matter than in superficial vascular structures.



Disclosures: **A. Taylor:** None. **X. Zou:** None. **J. Kim:** None. **D. Ress:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

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Program #/Poster #: 501.21/U28

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

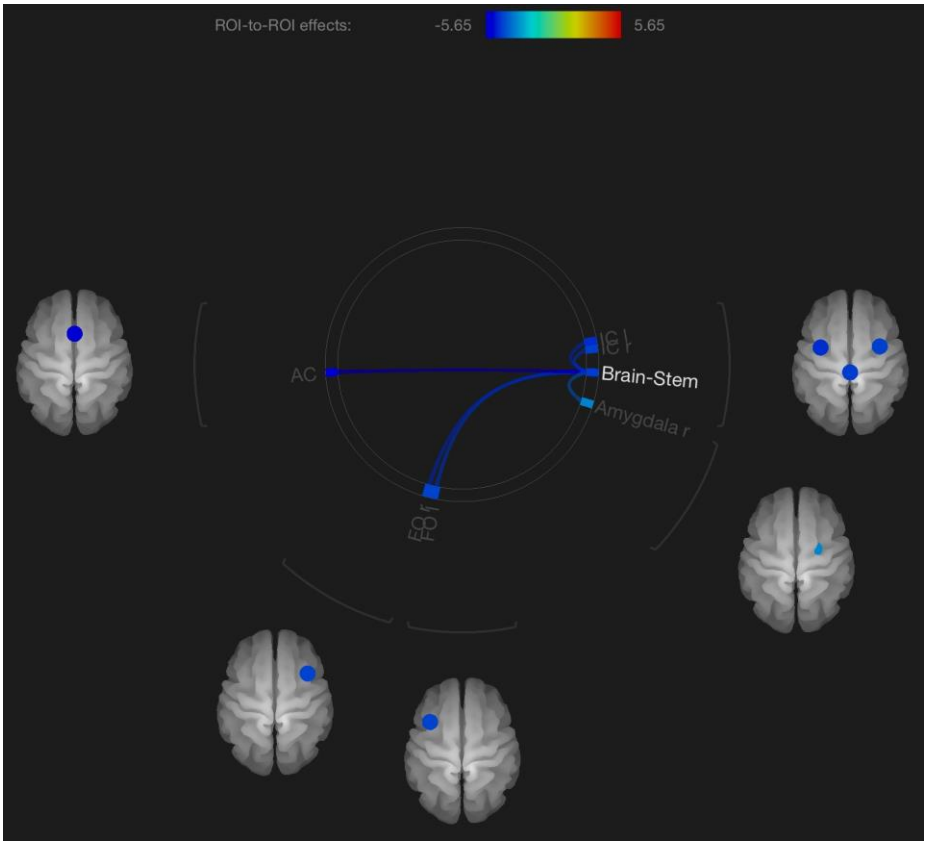
Support: Fonds de recherche Quebec santé - postdoctoral fellowship

Title: Disruption of midbrain functional connectivity in cerebral small vessel disease: Evidence from CADASIL

Authors: *D. SCHOEMAKER[1], Y. ZULUAGA[2], L. VELILLA[2], C. OSPINA[2], F. LOPERA[2], J. ARBOLEDA-VELASQUEZ[3], Y. T. QUIROZ[4];
[1]Psychiatry, Massachusetts Gen. Hospital/Harvard Med. Sch., Boston, MA; [2]Grupo de Neurociencias de Antioquia, Medellín, Colombia; [3]Schepens Eye Res. Inst., Boston, MA; [4]Massachusetts Gen. Hosp., Boston, MA

Abstract: The brain-stem is vulnerable to the effects of cerebral small vessel disease (SVD), a prevalent condition in the aging population that contributes to the risk of neurodegeneration and cognitive decline. However, the impact of SVD on brain-stem functional connectivity is undocumented. We examined resting-state functional connectivity in individuals with CADASIL, a hereditary condition caused by mutation on the NOTCH3 gene and leading to the early onset of SVD and vascular cognitive impairments.
Resting State fMRI was acquired in 25 individuals with CADASIL (mean age=50.52 +/-9) and 25 non-carriers (mean age=43.92 +/-10) and analyzed using *CONN* (Whitfield-Gabrieli et al., 2012). Functional connectivity between the brain-stem (seed region) and cortical regions-of-interest (ROIs) was compared between groups, while adjusting for age. Areas of significant between-group differences were identified using a stringent threshold (p-FDR=.01). Connectivity values in regions of significant differences were extracted for each subject, averaged across regions, and correlated with the overall volume of white matter lesions and cognitive performance.
Compared to non-carriers, CADASIL subjects showed reduced connectivity between the brain-stem and multiple cortical areas (Figure 1). Mean brain-stem connectivity was negatively correlated with age in CADASIL (r=-0.47, p=0.02), but not in non-carriers (p>.05). In CADASIL, mean brain-stem connectivity was associated with the volume of white matter lesions (r=-0.58, p=0.003), and performance on the INECO Frontal Screening (IFS, r=0.59, p=0.002) and the CERAD (r=0.51, p=01).
Overall our results showed a reduction in connectivity between the brain-stem and multiple cortical brain regions in CADASIL. Our results further revealed associations between brain-stem

connectivity, the burden of white matter lesion and cognition. Altogether, these findings suggest that SVD may contribute to early disruption in brain networks and onset of cognitive symptoms.



Disclosures: **D. Schoemaker:** None. **Y. Zuluaga:** None. **L. Velilla:** None. **C. Ospina:** None. **F. Lopera:** None. **J. Arboleda-Velasquez:** None. **Y.T. Quiroz:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.22/U29

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Title: Data quality and safety of simultaneous EEG-fMRI using multi-band fMRI sequences

Authors: *M. K. EGAN[1,2], R. LARSEN[2], B. P. SUTTON[2,3], S. SADAGHIANI[1,2];
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Abstract: Simultaneously recorded electroencephalography and functional magnetic resonance imaging (EEG-fMRI) is a highly informative imaging technique for brain function, but there exists little information about the data quality and safety when used with newer multi-band (MB) fMRI imaging sequences. As Brain Products (BP), manufacturer of MR-compatible EEG amplifiers, has no recommended MB protocol, we tested an MB sequence with lower radiofrequency deposition (RFD) than the nonMB sequence that they recommend. In a Siemens Prisma 3T scanner, we first tested an MB sequence (TR = 440 ms, flip angle = 40, nSlices = 28, MB factor = 4, GRAPPA factor = 2) against a modern nonMB sequence (TR = 1800ms, nSlices = 34, GRAPPA = 2) using only fMRI. Two pilot subjects underwent functional localizer tasks targeting auditory, face-selective, and emotion sensitive areas, once with each sequence. The MB sequence showed higher functional contrast than the nonMB sequence in both subjects, likely due to its high temporal and spatial resolution. Prior literature suggests that EEG electrode temperature is linearly proportional to RFD of concurrent fMRI. However, this literature did not include MB sequences, so we first examined the safety of electrode heating in the MB sequence. We compared the same MB sequence as above against the maximum intensity nonMB sequence considered safe for electrode heating in EEG-fMRI as recommended by BP (TR = 2000 ms, nSlices = 25) using 64 channel EEG on an impedance-matched head phantom. Temperature changes were measured by inserting Luxtron fluoroptic thermometer probes underneath ECG and TP7 (i.e. those with the longest leads / strongest RF absorption). Three 15-minute runs were acquired for each sequence, alternating in order, with a pause of 5 minutes between runs. The average temperature increase over the scanning period was a factor of 0.62 lower at ECG and 0.81 lower at TP7 for the MB than for the non-MB sequence, in accord with the calculated RFD. Next, we tested the EEG quality (64 channels, impedances <5 kOhm) using the MB sequence during a 10-minute eyes-closed resting state scan for 7 human subjects (4 females). Following MR and cardioballistic artifact rejection with procedures traditionally applied to nonMB sequences, spectrograms for all subjects showed a clear alpha peak at ~12Hz. Only a minimal peak remained in each spectrogram due to residual MR artifact at the RF repetition frequency. We conclude that EEG electrode heating for the above-described MB sequence is proportional to the calculated RFD and lower than the BP recommended nonMB sequence. The MB sequence provides high spatiotemporal resolution with no adverse effects on data quality.

Disclosures: **M.K. Egan:** None. **R. Larsen:** None. **B.P. Sutton:** None. **S. Sadaghiani:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.23/U30

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: MOST

Title: The effect of sleep deprivation on the brain-gut axis

Authors: *Y.-L. SHEN[1], D.-F. YANG[2], C. WU[1], Y.-T. TUNG[2];
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Abstract: Sleep deprivation is resulting from increased workload, shift work and various other challenges imposed by modern society may represent serious threat for health and well being. The increased BMI was seen when adult slept less than 7 hours per day. The impairment of spatial and emotional learning and memory can be detected after the deprivation of the slow-wave sleep and REM sleep in animals. In order to learn more about the effect of sleep deprivation on the physiology and brain of the organisms, the present study conducted the sleep deprivation by placing the mice on the grid over water for 72 h and collected the behavioral, biochemical changes and fMRI imaging thereafter. Firstly, our results showed that sleep deprived mice significantly reduced body weight and increased food intake. But their emotion and spatial learning were not affected by this stressful experience. We also found that the organ/body weight was increased in the kidney, but we did not see this in the liver, spleen and soleus. However, we did not detect any significant differences in the plasma biochemistries, such as AST, ALT, Albumin, LDH and CPK. For the fMRI, we did collect the activations in the visual cortex by manipulating the light stimulation in the mice subjects. Together, our results demonstrated that 72h on the grid over water is stressful for mice and this manipulation increased the weight of kidney. We did collect the light stimulation induced activation in mice in the fMRI and their resting-state fMRI remained to be determined.

Disclosures: Y. Shen: None. **D. Yang:** None. **C. Wu:** None. **Y. Tung:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.24/U31

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Science and Engineering Research Board (SERB) [YSS/2015/000734]

Title: Mapping brain hemodynamic signals and autonomic activity related to slow yoga breathing techniques and working memory performance

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Abstract: Yoga breathing is a slow, controlled and rhythmic activity which has been used for centuries to promote balance state of mind and cognitive processes. The combination of mental activity and slow breathing may influence cerebral oxygenation and autonomic nervous system activities. Therefore, the current study aimed to investigate the interaction between hemodynamic responses at the prefrontal cortex (PFC) and autonomic functions measured through heart rate variability (HRV) following a neurocognitive performance before and after yoga breathing practice. Forty healthy male volunteers were assessed during yoga breathing and spontaneous breathing sessions in two groups of yoga practitioners. The first group (n=20) received one-month yoga breathing orientation (YBO) at the rate of 6 breath per minute (bpm) over a period of one month before data collection and the second group (n=20) were assessed without any yoga breathing practice (NBT). The selected yoga practitioners had more than 12 months of experience, and none of them had any neurological or pathological conditions. We have used fNIRS to compare the relative changes in oxyhemoglobin (DHbO), deoxyhemoglobin (DHbR) and total hemoglobin (DTHb), in three yoga breathing practices *viz.* (i) left nostril breathing (LNB), (ii) right nostril breathing (RNB); and (iii) alternate nostril breathing (ANB) and compared with breath awareness (BAW). Relative changes in hemodynamic responses during yoga breathing sessions showed increased prefrontal oxygenation during ANB and RNB sessions that reflected in the improvement of participants performance in working memory task. The HRV results showed that all yoga breathing sessions at 6 bpm increases LF band, LF/HF ratio, mean HR, SDNN, TINN and decreases HF band, and mean RR. Moreover, the working memory performance was increased concomitantly with HRV, after RNB and ANB sessions. The outcome of the study suggests that yoga breathing enhances oxygenation at prefrontal PFC which is associated with better cognitive control over the task and parasympathetic withdrawal when compared with spontaneous breathing of BAW session. This indicates that yoga breathing enhances cognitive processes with better control over HRV.

Disclosures: S. Deepeshwar: None. **R.B. Budhi:** None. **T. Shetty:** None. **M.N. Krishnamurthy:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.25/U32

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: NIH Grant R01NS092388
NIH Grant U54GM104942

Title: Acute exposure to dim light at night is sufficient to induce neurological changes and depressive-like behavior

Authors: W. H. WALKER, II[1], J. C. BORNIGER[2], M. M. GAUDIER-DIAZ[3], O. H. MELÉNDEZ-FERNÁNDEZ2[1], J. L. PASCOE[1], A. C. DEVRIES[1], *R. J. NELSON[1]; [1]Neurosci., West Virginia Univ. Sch. of Med., Morgantown, WV; [2]Psychiatry & Behavioral Sci., Stanford, Stanford, CA; [3]Psychology & Neurosci., Univ. of North Carolina, Chapel Hill, NC

Abstract: The advent and wide-spread adoption of electric lighting over the past century has dramatically affected the circadian organization of physiology and behavior for many individuals in industrialized nations; electric lighting in homes, work environments, and public areas has extended daytime activities into the evening, thus, increasing night-time exposure to light. Although initially assumed to be innocuous, chronic exposure to light at night (LAN) is now associated with increased incidence of cancer, metabolic disorders, and affective problems in humans. However, little is known about potential acute effects of LAN. To determine whether acute exposure to low level LAN alters brain function, adult male and female mice were housed in either typical light days and dark nights (LD; 14h of 150 lux:10 h of 0 lux) or light days and low level light at night (LAN; 14h of 150 lux:10 h of 5 lux). Mice exposed to LAN on three consecutive nights increased depressive-like responses compared to mice housed in dark nights. Additionally, female mice exposed to LAN increased central tendency in the open field. LAN was associated with reduced hippocampal vascular endothelial growth factor-A (VEGF-A) in both male and female mice, as well as increased VEGFR1 and interleukin-1β mRNA expression in females and reduced brain derived neurotrophic factor mRNA in males. LAN significantly reduced active blood vasculature in the dentate gyrus, hilus, granular cell layer, and CA1, but not CA3 region of the hippocampus. Further, LAN significantly altered circadian rhythms (activity and temperature) and circadian gene expression in female and male mice respectively. Altogether, this study demonstrates that acute exposure to LAN alters brain physiology and can be detrimental to wellbeing in otherwise healthy individuals.

Disclosures: W.H. Walker: None. **R.J. Nelson:** None. **J.C. Borniger:** None. **M.M. Gaudier-Diaz:** None. **O.H. Meléndez-Fernández2:** None. **J.L. Pascoe:** None. **A.C. DeVries:** None.

Poster

501. Functional Brain Imaging and Multimodal Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 501.26/U33

Topic: F.06. Brain Blood Flow/ Metabolism/ and Homeostasis

Support: Medical Research Council (MRC) UK Grant Number MR/M013553/1
Alzheimer's Research UK (ARUK) Grant Number ARUK-IRG2014

Title: Neurovascular function in J20 Alzheimer's mice and cardiovascular disease/mixed dementia mouse models

Authors: *O. SHABIR, P. S. SHARP, B. J. PENDRY, M. L. FLOARE, C. HOWARTH, P. HEATH, J. SIMPSON, S. B. WHARTON, S. E. FRANCIS, J. BERWICK;
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Abstract: Background: Neurovascular coupling is the mechanism by which the brain regulates cerebral blood flow to localised neural activity. The breakdown of this relationship can trigger or contribute to many neurological conditions, including Alzheimer's disease (AD).
Aims: Firstly, to investigate neurovascular function in young AD mice. Secondly, to investigate if neurovascular function in mid-age atherosclerotic and mixed-dementia mouse models is altered.
Methods: 6-9m male WT C57BL/6J mice (n=8) and J20-hAPP (n=9) mice were used to investigate early-AD. 9-12m male WT C57BL/6J (n=4), J20-hAPP (n=4), rAAV8-mPCSK9-D377Y + Western Diet (n=5) and rAAV8-mPCSK9-D377Y-J20-hAPP + Western Diet (n=3) were used. Briefly, a thinned cranial window surgery was performed to reveal cortical vessels. Mice were recovered for 2-weeks before imaging. Animals were anaesthetised and imaged using 2D-optical imaging spectroscopy. Mechanical whisker stimulations of either 2s or 16s were performed under 100% oxygen and 21% oxygen conditions. A week later, a final imaging session was performed where an electrode was inserted into the cortex to record neural responses and haemodynamics simultaneously. At the end of terminal acute experiments, mice were transcardially perfused with saline and the brains were dissected for immunohistochemistry and gene expression studies.
Findings: Blood volume (HbT) is significantly higher in 6-9m J20 mice compared to WTs in response to stimulations (p=.004). Furthermore, under 100% oxygen, the baseline HbT is significantly higher in J20's (p=.0005), with significant arterial and venous dilation, compared to WTs. When transitioning from 100% oxygen to 21% oxygen, there is a decrease in HbT in J20s, but not WTs. Finally, stimulation-evoked multi-unit activity is significantly higher in J20s (p=.0001) compared to WTs. In the second study, we see a reduction of HbT in mPCSK9-atherosclerotic mice, in response to stimulations. The mPCSK9-J20 mixed dementia mouse models show significant perturbations to physiological stimulations, which worsen under 21% oxygen (mild gas challenge) conditions.
Conclusions: The neural abnormalities coupled with haemodynamic differences could serve to be effective biomarkers in certain forms of AD, and point towards a potential therapeutic strategy. Secondly, we have novel insights into how cardiovascular disease can affect cerebral haemodynamics and the brain as a whole.

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Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.01/U34

Topic: F.08. Biological Rhythms and Sleep

Title: Multitaper spectrograms reveal opiate specific changes in mouse electroencephalogram

Authors: *C. B. O'BRIEN[1], C. E. LOCKLEAR[1], Z. T. GLOVAK[1], H. A. BAGHDOYAN[1,2,3], R. LYDIC[1,2,3];
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Abstract: Electroencephalographic (EEG) data traditionally have been analyzed in the frequency domain to characterize levels of behavioral and neurophysiological arousal (*J Vis Exp* 117: e54908, 2016). The multitaper spectrogram transforms EEG waveforms into time and frequency domains. This enables visualization of state-dependent changes in EEG power and frequency (*Physiology* 32: 60, 2017). The present study is testing the hypothesis that intraperitoneal injection of the opiates buprenorphine, morphine, and fentanyl differentially alters EEG activity in C57BL/6J (B6) mice. Adult males (n = 4) were anesthetized and implanted with telemeters (DSI HD-X02) connected to cortical EEG electrodes and neck muscle electromyogram (EMG) electrodes. The recordings of EEG and EMG activity were wirelessly transmitted from freely behaving mice and used to objectively score states of sleep and wakefulness for 4 h after injection of saline (vehicle control) and antinociceptive doses of each opiate (see companion abstract by C. E. Locklear et al). The results revealed unique features in the cortical EEG caused by the different opiates. Buprenorphine and morphine caused similar changes in the spectrograms relative to saline, with increases in EEG power at 1 to 3 Hz and 8 to 9 Hz. Spectrograms after administration of fentanyl were most similar to spectrograms recorded after saline, with maximal average power bands at 3 Hz and 7 Hz. The EEG power distributions were further analyzed across frequency bands including delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), and beta (13-30 Hz). Compared to EEG power measured after saline administration, the percent change in power was differentially altered by buprenorphine: delta -64, theta -89; alpha 140, beta -43; morphine: delta -55, theta -86, alpha 58, beta 5; and fentanyl: delta -65, theta -76, alpha -22, beta -57. ANOVA revealed that EEG power in the delta, theta, and alpha bands was significantly ($p<0.01$) different from EEG power after saline for all three opiates. There was not a significant power change in EEG beta. Multiple comparisons tests revealed that EEG power was significantly ($p=0.03$) different between buprenorphine and fentanyl in theta and alpha bands. Multitaper spectrograms provide a nuanced perspective of EEG traits that characterize obtunded states of wakefulness and the inhibition of NREM and REM sleep caused by opiates.

Ongoing studies are increasing the number of mice. Future studies will quantify state-dependent variations in EEG spectrograms caused by chronically administered opiates.

Disclosures: C.B. O'Brien: None. **C.E. Locklear:** None. **Z.T. Glovak:** None. **H.A. Baghdoyan:** None. **R. Lydic:** None.

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.02/U35

Topic: F.08. Biological Rhythms and Sleep

Title: Systemically administered opiates disrupt the architecture of sleep and wakefulness in mouse

Authors: *C. E. LOCKLEAR[1], C. G. BUSTAMANTE[1], Z. T. GLOVAK[1], D. ZEBADUA UNZAGA[1], C. B. O'BRIEN[1], R. LYDIC[1,2,3], H. A. BAGHDOYAN[1,2,3];
[1]Psychology, [2]Anesthesiol., Univ. of Tennessee, Knoxville, TN; [3]Oak Ridge Natl. Lab., Oak Ridge, TN

Abstract: Opioid use disorder (OUD) is a major public health burden yet the opiate buprenorphine is FDA-approved for treatment of OUD. Opiates long have been shown to disrupt sleep, and sleep disruption enhances the likelihood of addiction relapse in humans (*Med Hypotheses* 74: 928, 2010). The current study is testing the hypothesis that acute administration of buprenorphine, morphine, and fentanyl differentially alters sleep/wake architecture in C57BL/6J (B6) mice. Adult males (n = 4) were housed in a temperature-controlled environment and a 12:12 light:dark cycle with ad libitum access to food and water. Mice were anesthetized with isoflurane for implantation of a telemeter (DSI HD-X02) and electrodes for recording cortical electroencephalogram (EEG) and dorsal neck muscle electromyogram (EMG). These signals were used to objectively quantify states of wakefulness, NREM sleep, and REM sleep in 10-s bins. Recordings began two weeks after the mice recovered from surgery. Every mouse received at least one intraperitoneal injection (0.3 mL) each of saline (vehicle control) and an antinociceptive dose of buprenorphine, morphine, and fentanyl. Injections were performed within 90 min of light onset. Repeated injections in the same mouse were separated by at least one week. Each 4-h recording was scored independently by two individuals, one of whom was blinded to the treatment condition. Sleep scoring concordance was greater than 90%. Data from repeated injections of the same drug into the same mouse were averaged in order not to inflate degrees of freedom. These preliminary results, expressed as percent change from saline, summarize 29 recordings. Buprenorphine increased wakefulness (190%), eliminated NREM sleep, and eliminated REM sleep. Morphine increased wakefulness (167%), decreased NREM sleep (-87%), increased latency to onset of NREM sleep (357%), and eliminated REM sleep.

Fentanyl increased wakefulness (105%), decreased NREM sleep (-54%), increased NREM sleep latency (193%), decreased REM sleep (-69%), and increased REM sleep latency (39%). The three opiates also differentially altered EEG power (see companion abstract C.B. O'Brien et al). These emerging results support the hypothesis that buprenorphine, morphine, and fentanyl differentially alter sleep/wake architecture in male B6 mice. Ongoing studies are increasing sample size and evaluating the extent to which opiate-induced sleep disruption is dose dependent and blocked by naloxone. Future studies will evaluate sex as an independent variable in B6 mice and mice with diet-induced obesity, as well as effects of chronic opiate administration on sleep/wake architecture.

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Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.03/U36

Topic: F.08. Biological Rhythms and Sleep

Support: State of Washington Initiative Measure No. 171

Title: Sleep improves when hyperbaric oxygen therapy administered before and after methadone dose reduction for adults with opioid use disorder

Authors: *R. M. QUOCK[1], M. WILSON[2], L. SKEIKY[3], K. STANEK[5], T. ODOM-MARYON[2], D. HANSEN[3], M. LAYTON[4];
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Abstract: Sleep disturbances are a significant problem for adults prescribed opioids for pain control and medication-assisted treatment for opioid use disorder [Cheatle and Webster, *Pain Med*, 16:S22-S26, 2015; Sharkey *et al*., *Drug Alcohol Depend*, 113:245-248, 2011]. As much as 80% of adults enrolled in medication-assisted behavioral treatment for opioid use disorder report reduced sleep quality and quantity [Sharkey *et al*., *Drug Alcohol Depend*, 113:245-248, 2011], which can interfere with substance use recovery goals [Stein *et al*., *J Subst Abuse Treat*, 26:175-180, 2004]. Preclinical research has found that HBOT—100% oxygen at greater-than-atmospheric pressure—suppresses physical signs of naloxone-precipitated withdrawal in morphine-dependent mice [Nicoara *et al*., *Brain Res* 1648:434-437, 2016]. HBOT has been shown to improve self-report and objective measures of sleep in human subjects being treated for various illnesses [Uezato *et al*., *Psychiatry Clin Neurosci* 71:73-74, 2016; Long *et al*., *Neurol*

Res 39:239-247, 2017]. In order to investigate the role of HBOT on self-report and objective measures of sleep in adults with opioid use disorder, 31 participants (11 males, 20 females) were randomized into HBOT (n=17) or control (n=14) arms. HBOT was administered for five consecutive days in 90-min sessions at 2.0 atmospheres absolute with 100% oxygen via individualized oxygen hoods in a 12-seat sealed, pressurized chamber. Participants agreed to a 10% reduction in current methadone dose or 5 mg, whichever was smaller, to occur on Day 2 after HBOT pretreatment on Day 1. The short-form PROMIS Sleep Disturbance scale, an assessment of self-reported sleep quality (*e.g.*, trouble falling asleep, feeling rested, restless sleep), was the primary sleep measure collected at baseline, and post-treatment at 1 week, 1 month, and 3 months. For a sub-sample (n=7) of those in the HBOT arm, objective sleep measures were captured one week pre- and post-HBOT via wrist-worn actigraphy. PROMIS Sleep Disturbance results showed that the mean sleep disturbance for the control group increased from baseline to post-intervention at each measurement timepoint while it trended downward for the HBOT group, indicating less sleep disturbance at each timepoint after HBOT. Post-treatment actigraphy results support the self-report findings, showing an approximate 30-min increase in total sleep time and a 10-min reduction in sleep onset latency in the week following HBOT. These findings support the working hypothesis that clinically significant improvements in sleep duration and time to fall asleep are possible when HBOT is administered before and after opioid dose reduction.

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Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.04/U37

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant NS078498-05A1

Title: Antioxidant supplementation augments gamma activity during sleep deprivation

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Abstract: Cognitive impairment is one of the most robust and reliable indicators of sleep deprivation (SD), impacting tasks that require sustained attention, memory, and performance. Such demanding attentional tasks are mediated by gamma oscillations (60-90 Hz) in the waking brain. Gamma oscillations are also compromised by sleep deprivation and byproducts of

oxidative metabolism, which build up in the brain during periods of prolonged wakefulness. Our current studies assess the efficacy of long- and short-term exogenous antioxidant treatments in mitigating gamma-suppressing effects of sleep deprivation. In the long-term supplementation study, adult mice (12 weeks old; n=23) were placed on a control or antioxidant-enriched diet (nicotinamide riboside [NR]; 400 mg/kg/day) for 10 weeks. At 14 weeks of age, mice were instrumented for sleep recordings. Baseline and sleep-deprived recordings were taken at 4, 6, 8, and 10 weeks on diet to assess the effect of accumulating NR on sleep parameters. The second study demonstrates the effects of short-term antioxidant supplementation via intraperitoneal injections of N-acetylcysteine (NAC; 600mg/kg/injection) in adult mice (12 weeks old; n=25). Baseline and sleep deprived recordings were taken on the day of NAC administration. While no changes were observed in sleep architecture with either treatment (i.e. sleep fragmentation or distribution of sleep throughout the 24-hour day), gamma activity increased during sleep deprivation in mice undergoing either antioxidant supplementation. After 6 weeks on NR-enriched diet, mice demonstrated roughly two-fold increases in gamma oscillations (measured in $\mu V^2/Hz$) during SD when compared with SD mice on an isocaloric control diet. This change persisted through week 10 of the dietary manipulation. NAC also produced nonsignificant increases in gamma oscillations during SD within an hour of administration ($p>0.05$). Collectively, our data indicate that prophylactic treatments that are capable of increasing antioxidant defense in the brain (NAC and NR) may preserve brain function during and after sleep deprivation, potentially staving off sleep deprivation-related cognitive impairment.

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Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.05/U38

Topic: F.08. Biological Rhythms and Sleep

Support: Cariverona Foundation PhD Fellowship awarded to MB
Wellcome Trust 215267/Z/19/Z awarded to MB

Title: Sleep loss increases membrane fluidity of myelin sheaths

Authors: A. ABOUFARES EL ALAOUI[1], R. FIORINI[2], M. FABRI[1], ***M. BELLESI**[3]; [1]Dept. of Exptl. and Clin. Med., [2]Dept. of Life and Envrn. Sci., Marche Polytechnic Univ., Ancona, Italy; [3]Sch. of Physiology, Pharmacol. & Neurosci., Univ. of Bristol, Bristol, United Kingdom

Abstract: Using electron and confocal microscopy we recently showed that prolonged sleep restriction (~5 days) reduced myelin thickness and increased node of Ranvier length without

affecting internodal length, thus suggesting that sleep loss can lead to plastic remodeling of myelin. Since optimal plasma membrane fluidity is an essential requirement for cellular plasticity, we hypothesized that the fluidity of membranes forming myelin could be affected by sleep loss. Membrane fluidity of myelin enriched brain samples from sleeping (S, n=6, killed after 6 hrs of sleep during the light cycle) and sleep deprived C57BL/6 mice (SD, n=6, killed after 4 hrs of enforced wake during the light cycle) was assessed by steady-state fluorescence spectroscopy. Two fluorophores were used, 2-dimethylamino-(lauroyl)-naphtalene (Laurdan) located at hydrophobic-hydrophilic interface of the membrane, and 1,6 diphenyl-1,3,5-hexatriene, incorporated in hydrophobic lipid region. Moreover, in mouse forebrain samples, genome-wide analysis of messenger RNA profiling of oligodendrocyte lineage was conducted as a function of S and SD to detect differentially expressed genes. A significant increase in membrane fluidity was found in myelin membrane core in SD relative to S (DPH anisotropy: S [0.231±0.008]; SD [0.222±0.005], $p<0.00019$), while no differences were detected at the polar headgroups level. In addition, analysis of the oligodendroglia transcriptome revealed the up-regulation of *Fad3* in SD (+176%; p=0.004). *Fad3* codes for a fatty acid desaturase that regulates unsaturation of fatty acids and thus influences membrane fluidity. In conclusion, increased fluidity of the inner myelin membrane region could contribute to morphological modifications of myelin induced by sleep loss.

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Poster

502. Impacts of Sleep Disruption

Location: Hall A

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Program #/Poster #: 502.06/U39

Topic: F.08. Biological Rhythms and Sleep

Support: NIH 1F30HL145901-01
NIH 5R01HL129138-04

Title: Estradiol action modulates adenosinergic sleep pressure

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Abstract: Primary sleep disorders are among the most common medical conditions, and clinically, women are more likely than men to experience symptoms of insomnia over their lifespan. This increased risk emerges at puberty and is associated with fluctuations in ovarian

steroids, particularly estradiol (E2), suggesting that gonadal steroids and biological sex are risk factors for sleep disruptions. In female rodents, studies consistently show sleep time is significantly reduced when endogenous ovarian steroids or exogenous E2 are elevated. Our work has demonstrated that E2 effects on sleep are mediated through the inhibition of sleep-active neurons in the median preoptic nucleus (MnPN). However, what is less clear is how E2 is suppressing sleep; one potential mechanism is the attenuation of signaling pathways necessary for maintaining sleep homeostasis. To test this possibility, we sleep deprived oophorectomized rats, with and without E2 replacement, for three or six hours by gentle handling, and quantitatively analyzed sleep behavior and power spectra for the subsequent six hours of recovery. We found that E2-treated animals require less recovery sleep under deprivation, and show a greater increase in delta power, a measure of sleep efficiency, relative to baseline. The nucleoside adenosine is a mediator of homeostatic sleep pressure, with established actions at the MnPN. Next, we tested the hypothesis that E2 attenuates the ability of adenosine signaling to stimulate sleep behavior in female rats. Oophorectomized rats were treated with a constant low-dose of E2, which was not sufficient to suppress sleep, or oil vehicle. Following a baseline recording, animals were treated with injections of 24nmol of the adenosine 2A receptor agonist CGS21680, at a dose sufficient to induce sleep in male animals, or DMSO vehicle, with animals receiving the opposite treatment three days later. Sleep behavior was analyzed six hours following each injection. In the oil treated animals, the infusion of agonist led to a decrease in wake time as expected. However, in the E2 group, the effect of the agonist on wake time was significantly attenuated. Studies are ongoing to determine if the amount of extracellular adenosine present in the MnPN differs with and without E2. These data suggest the ability of adenosine to generate sleep pressure, and the effect of E2 on wake, are modulated by an interplay between estrogen and adenosine.

Disclosures: P.C. Smith: None. **D.J. Phillips:** None. **S.S. Viechweg:** None. **A. Pocivavsek:** None. **J.A. Mong:** None.

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.07/U40

Topic: F.08. Biological Rhythms and Sleep

Title: SUVN-G3031, histamine H3 receptor inverse agonist preclinical evaluation for the treatment of excessive daytime sleepiness in narcolepsy

Authors: *G. BHYRAPUNENI, V. BENADE, S. DARIPELLI, V. KAMUJU, A. SHINDE, R. ABRAHAM, R. NIROGI, V. JASTI;
Suven Life Sci. Ltd., Hyderabad, India

Abstract: Numerous studies have demonstrated that brain histamine plays a crucial role in maintenance of wakefulness, attention, learning and other cognitive processes. SUVN-G3031, a potent histamine H3 receptor inverse agonist is being developed for the treatment of narcolepsy and other sleep related disorders. SUVN-G3031 is one of the lead molecules with hKi of 8.7 nM and has more than 100 fold selectivity against the related GPCRs. SUVN-G3031 exhibited desired pharmacokinetic properties and brain penetration. SUVN-G3031 blocked R-α-methylhistamine induced water intake and increased tele-methylhistamine levels in brain and cerebrospinal fluid. In the present study, SUVN-G3031 was evaluated in brain microdialysis and rodent models of electroencephalography (EEG). SUVN-G3031 was evaluated in brain microdialysis for evaluation of neurotransmitters like acetylcholine, histamine, dopamine and norepinephrine in male Wistar rats. EEG was used to evaluate the effects on sleep/ wake profile in rats and mice.A single oral administration of SUVN-G3031 produced significant increase in acetylcholine, histamine, dopamine and norepinephrine levels in the cortex. SUVN-G3031 produced no change in the dopamine levels of striatum and nucleus accumbens indicating that SUVN-G3031 may not have addiction liabilities. Narcoleptic-like sleep behavior was observed in rats injected with hypocretin-2-saporin in lateral hypothalamus. SUVN-G3031 produced significant increase in wakefulness with concomitant decrease in rapid eye movement (REM) sleep in these animals. These results are in agreement with EEG studies carried out in healthy male Wistar rats. Results from current studies provide strong evidence for the potential of SUVN-G3031 in the treatment of excessive daytime sleepiness associated with narcolepsy. First in human, Phase 1 studies for SUVN-G3031 are completed under US IND and SUVN-G3031 has shown desirable pharmacokinetic profile with safety and tolerability in healthy human volunteers. Phase 2 study for the treatment of excessive daytime sleepiness associated with narcolepsy is currently ongoing in USA.

Disclosures: **G. Bhyrapuneni:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Benade:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **S. Daripelli:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Kamuju:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **A. Shinde:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **V. Jasti:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd..

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.08/V1

Topic: F.08. Biological Rhythms and Sleep

Title: Melatonin and recovery sleep ameliorate anxious behaviour and impairment in hippocampal neurogenesis induced by sleep deprivation

Authors: *R. CHITTORA[1], A. JAIN[2], M. BHATNAGAR[1];
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Abstract: Abstract
Sleep deprivation (SD) is commonplace occurrence in modern society. SD is associated with reduced short term memory, learning ability and loss of some forms of behavioral control. Thus, we hypothesized that whether sleep deprivation would impact learning-induced neurogenesis in concert with its behavioural outcome which could be improved by administering natural antioxidant and Enriched environment. The aim of this study was to assess the effect of melatonin and subsequent recovery sleep on adult neurogenesis in the hippocampus and behaviour of adult mice exposed to 6 days of total sleep deprivation (TSD). Adult male Swiss Albino mice were sleep deprived for 6 days using manually designed SD apparatus. Melatonin (10 mg/kg BW/day) was administered intraperitoneally to mice once every day during SD. Some mice received additional recovery sleep for 2 days after 6 days TSD. Adult neurogenesis was assessed by Immunohistochemical markers Doublecortin (DCX), neuronal nuclei antigen (NeuN) and anxious behaviour was evaluated by Open Field Test and Elevated plus Maze Test. Immunohistochemical analysis demonstrated that SD reduced the number of migrating neuroblasts and immature neurons i.e. DCX positive cells in dorsal and ventral blades of Dentate Gyrus. SD also decreased number of NeuN+ mature neuronal cells in CA1, CA3, DG sub region of hippocampus. Sleep deprived mice presented an increased number of entries and time spent in closed arms in elevated plus maze test and decreased center square entries, Reduced rearing, Grooming and increased Fecal boli counts in the open field test. Melatonin co-administration and recovery sleep significantly improved these neurogenesis and anxious consequences. These findings reveal that exogenous administration of melatonin and environmental enrichment induced recovery sleep have the potential to diminish the negative effects of SD on neurogenesis and behavior.

Disclosures: R. Chittora: None. **A. Jain:** None. **M. Bhatnagar:** None.

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.09/V2

Topic: F.08. Biological Rhythms and Sleep

Support: NIH R01 NS102209

Title: Differential impact of light or dark phase kynurenine challenge in male and female rats: Biochemical alterations and disruptions in sleep-wake behavior

Authors: A. M. LEWIS[1], N. T. J. WAGNER[1], K. M. RENTSCHLER[1], S. A. BUCK[2], A. BARATTA[4], S. BEGGIATO[5], J. A. MONG[3], ***A. POCIVAVSEK**[1];
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Abstract: Tryptophan metabolism via the kynurenine pathway (KP) may represent a key molecular link between sleep loss and cognitive dysfunction. Modest increases in the KP metabolite kynurenic acid (KYNA), which acts as an antagonist at N-methyl-D-aspartate (NMDA) and α7 nicotinic acetylcholine (α7nACh) receptors, and an agonist at the aryl hydrocarbon (AhR) receptors, result in cognitive impairments. These disruptions may be causally related to impairments in sleep-wake behavior with KYNA elevation (Pocivavsek et al. Sleep, 2017). Presently, we further explored this hypothesis in adult cohorts of both male and female Wistar rats. In consideration of the circadian rhythm, animals were treated with vehicle or kynurenine (100mg/kg; intraperitoneally), the direct precursor to KYNA, at the beginning of the light phase, zeitgeiber time (ZT) 0, or at the beginning of the dark phase, ZT12. *In vivo* microdialysis, collected from the dorsal hippocampus in 30-min fractions, confirmed significant formation of KYNA with kynurenine challenge during both phases. In controls, we demonstrate a phase x time interaction (**P<0.0001) and a significant main effect of time (**P<0.01). Specifically, extracellular KYNA levels decreased across time in the light phase and increased across time in the dark phase. In separate animals, we acquired polysomnographic recordings that combine electroencephalogram (EEG) and electromyogram (EMG). Animals were treated with vehicle or kynurenine at ZT 0 or ZT 12, respectively. Analysis of vigilance state-related parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed for 24 h after treatment. Kynurenine treatment at ZT 0 significantly reduced REM duration compared to vehicle treatment (*P<0.05) during the 12 h of the light phase in both male and female rats. Conversely, kynurenine treatment at ZT 12 did not immediately impact vigilance state duration during the 12 h of dark phase, but significantly affected REM duration, in males only, during the subsequent light phase (*P<0.05). Separate animals were tested in the novel object recognition (NOR) task assessing hippocampal-dependent recognition memory. Task performance was negatively impacted by kynurenine challenge during both light and dark phase. Taken together, our results and future complementary experiments provide significant mechanistic value to understanding the role of KYNA in modulating a relationship between sleep, circadian systems and cognition.

Disclosures: **A.M. Lewis:** None. **N.T.J. Wagner:** None. **K.M. Rentschler:** None. **S.A. Buck:** None. **A. Baratta:** None. **S. Beggiato:** None. **J.A. Mong:** None. **A. Pocivavsek:** None.

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.10/V3

Topic: F.08. Biological Rhythms and Sleep

Support: NIH NS102209

Title: An experimental system of prenatal kynurenine elevation: Distinct sex-dependent alterations in brain kynurenic acid and sleep disturbances in adulthood

Authors: *K. RENTSCHLER[1], A. BARATTA[2,3], A. L. DITTY[1], A. M. LEWIS[1], N. T. J. WAGNER[1], C. J. WRIGHT[1], J. A. MONG[4], A. POCIVAVSEK[1,3];
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Abstract: Dysfunction in the kynurenine pathway (KP) of tryptophan metabolism has been implicated in the pathology of schizophrenia (SZ). The KP metabolite kynurenic acid (KYNA) is an endogenous antagonist of α7 nicotinic acetylcholine (α7nACh) and N-methyl-D-aspartate (NMDA) receptors, and an activator of aryl hydrocarbon receptors (AhR). KYNA has been linked to cognitive impairments in SZ and may also contribute to sleep disturbances in patients. To further understand the role of KYNA in SZ etiology, we developed an experimental system in rats (Pocivavsek et al., *Psychopharm.*, 2014) where kynurenine (kyn; 100 mg/day) is fed to pregnant Wistar dams from embryonic day (ED) 15 to ED 22 (control: ECon; kyn-treated: EKyn) to elevate KYNA in the fetal brain. The present study was designed to investigate 1) KP metabolism during the light (ZT6) and dark phase (ZT18) and 2) sleep-wake behavior during both phases in male and female adult (postnatal day 56 -85) offspring from ECon and EKyn litters. Cortical KYNA levels were increased (+128%) at ZT6 in male, but not female, EKyn compared to ECon (**P<0.01). No differences were found at ZT18. Adult offspring were implanted with telemetric devices to acquire polysomnographic recordings to combine electroencephalogram (EEG) and electromyogram (EMG) readings (N=6-8 per group). Analyses of vigilance state parameters categorized as wake, rapid eye movement (REM) and non-REM (NREM) were assessed. Our findings indicate distinct sex differences in sleep disturbances among ECon and EKyn offspring. EKyn males had significantly less REM duration during the light phase (*P<0.05, -21%). EKyn females had less frequent wake bouts (*P<0.05, -30%), which were also longer in duration (***P<0.001, +37.5%), and less frequent NREM bouts (*P<0.05, -28%) during the dark phase. Delta and theta power were assessed during each vigilance state to define deficits in sleep oscillations. Taken together, our data demonstrate a striking sex- and light phase-dependent increase in cortical KYNA and sleep alterations in EKyn

offspring. We are continuing to investigate elevated prenatal kynurenine exposure to further understand the interplay between KP metabolism in psychiatric illness, sleep disturbances, and cognitive outcomes.

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Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant DP2MH104119
Human Frontiers Science Program N023241-00
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Title: Regulation of pS6 and Arc in the hippocampus by sleep and learning

Authors: ***V. K. KODOTH**[1], J. DELORME[1], S. J. ATON[2];
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Abstract: The activity-regulated cytoskeleton associated protein (Arc) is an immediate early gene whose mRNA accumulates in recently-activated neurons, where it can undergo activity-dependent translation to affect synaptic function. Recent data from our lab has shown that after a brief period of sleep deprivation (relative to a similar period of ad lib sleep), there is increased total Arc mRNA in the hippocampus but decreased Arc protein-expressing neurons in the dentate gyrus of the hippocampus. At the same time, sleep deprivation increases both Arc mRNA and protein in the cortex. This suggests that sleep may play a role in promoting translation of Arc protein in the hippocampus, which may have a major impact on sleep-dependent memory processes. Moreover, protein synthesis may be generally reduced in the hippocampus during sleep deprivation. Ribosomal subunit S6 is phosphorylated on several serine residues by activity-regulated kinases; these phosphorylation events are thought to regulate translation by the ribosome. Here we characterize the degree of phosphorylation of S6 on sites targeted by neuronal activity (pS6 244-247) within the hippocampus. We find that over 3 hour periods of sleep deprivation, there is a selective reduction of S6 phosphorylation in the cell bodies of hippocampal subregions CA1 and CA3, and in dentate gyrus (DG) neurons. We also quantify colocalization between Arc protein and pS6 244-247 throughout the hippocampus. pS6 244-247 and Arc colocalize in dentate gyrus neurons in both sleep and sleep deprived animals, although total levels of both are reduced after sleep deprivation. These findings better characterize the cellular mechanisms that may disrupt hippocampal memory consolidation during sleep loss.

Disclosures: **V.K. Kodoth:** None. **J. Delorme:** None. **S.J. Aton:** None.

Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: I01 BX001404
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I01 BX001356
I01 BX002774
IK2 BX002130
R21 NS079866
R01 MH039683

Title: Neural substrates underlying the homeostatic sleep response in mouse basal forebrain

Authors: C. YANG[1], H. BOUAOUDA[1], C. SHUKLA[1], K. DEISSEROTH[2], S. WINSTON[1], Y. BOLORTUYA[1], J. M. MCNALLY[1], J. T. MCKENNA[1], ***R. BASHEER**[1];
[1]Psychiatry, VA Boston Healthcare System-Harvard Med. Sch., West Roxbury, MA; [2]Bioengin & Psych, Stanford Univ. Dept. of Psychology, Stanford, CA

Abstract: Optogenetic stimulation of cholinergic (ChAT+), vesicular glutamate transporter2-expressing glutamatergic (vGluT2+) or parvalbumin-expressing GABAergic (PV+) neurons in the basal forebrain (BF) cause arousal responses. However, little is known about their role in the homeostatic sleep response (HSR). BF ChAT+ neurons are thought to play a privileged role in HSR, since selective lesions of these neurons abolish the HSR. Previous *in vitro* work from our and other laboratories have revealed local interaction among BF ChAT+, vGluT2+ and PV+ neurons. Here, we explore the interactive role of BF ChAT+ and vGluT2+ neurons as well as PV+ neurons in HSR using *in vivo* pharmacological and optogenetic approaches combined with conventional electroencephalogram/electromyogram recordings. C57BL/6 (WT) mice were sleep deprived (SD) 6h with and without reverse microdialysis of cholinergic or glutamate receptors antagonists into BF to examine the effect of pharmacological blockade of the cholinergic and glutamatergic receptors on rebound recovery sleep and non-rapid-eye-movement (NREM) delta activity (0.5-4.5Hz), the markers of HSR. We transduced AAV-ChR2-EYFP in BF of ChAT-Cre, vGluT-Cre and PV-Cre mice and examined the effect of 4-6h optical stimulation (5s/min, 10 Hz for ChAT+, 20 Hz vGluT2+ and 40Hz for PV+) on HSR during the 2h post-stimulation period by comparing to time-matched sham stimulation. Furthermore, we performed microdialysis of cholinergic/glutamatergic receptor antagonists during the optical stimulation of ChAT+/vGluT2+ neurons and examined the HSR. In WT mice (n=4) cholinergic antagonists did

not prevent SD-induced HSR as evaluated by an increased sleep (+36.74±5.65%) and the NREM delta power (+13.82±3.62%). Microdialysis of AMPA or NMDA receptor antagonists in another set of WT mice (n=3) showed a tendency towards attenuated recovery sleep by -5.06±7.35% and -11.72±4.05%, respectively. Optogenetic stimulation of ChAT+ neurons (n=3) as well as vGluT2+ neurons (n=3) led to HSR. While cholinergic receptor antagonist failed to block cholinergic neuronal activation-induced HSR, the glutamatergic receptor antagonists attenuated glutamatergic neuronal activation-induced HSR. PV+ neuronal-stimulations failed to induce HSR. Our preliminary results suggest that both BF cholinergic and glutamatergic neurons, are important for HSR. BF glutamatergic neurons induce HSR by acting on local cholinergic neurons while other BF non-cholinergic neurons (PV+) are unlikely to play any role in HSR.

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Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.13/V6

Topic: F.08. Biological Rhythms and Sleep

Support: Rut and Arvid Wolff Memorial Foundation
Swedish research council
Hjärnfonden

Title: Sleep deprivation and how it affects the neuropil

Authors: S. GABULYA[1], A. T. BRODIN[1], L. OLSON[2], ***T. E. KARLSSON**[1];
[1]Neurosci., Karolinska Institutet, Solna, Sweden; [2]Dept. of Neurosci., Karolinska Inst., Solna, Sweden

Abstract: Sleep deprivation is a common problem and often occurs as a part of a bigger disease spectrum such as depression or PTSD. Contrary to common belief, sleep is a rather active time window during which many functions in the central nervous system are carried out. Among these are clearing of waste products and replay and stabilization of memories. Disruptions of these processes, as caused by sleep deprivation, has severe consequences such as impaired memory function. There have been recent reports by others suggesting that the structure of neurons can change dramatically during situations of sleep deprivation. We studied this further using THY1-GFP mice and light sheet microscopy. Mice were subjected to sleep deprivation for five hours using a gentile method of manually pushing on mice that tended to fall asleep. These mice were compared to two other groups, one that underwent the same episode of sleep deprivation but then

allowed to have three hours of recovery sleep and a control group that did not receive sleep deprivation. We then analyzed the branching pattern of the apical dendrites of CA1 pyramidal neurons in hippocampus. Overall, neither the length, nor the branching pattern of the apical dendrite was affected by sleep deprivation. We conclude that 5 h of (gentile) sleep deprivation does not cause overt alterations of dendritic length or branching patters of hippocampal CA1 pyramidal cells. Ongoing work will analyze a possible role of sleep deprivation on spine density in the same neurons.

Disclosures: **S. Gabulya:** None. **A.T. Brodin:** None. **L. Olson:** None. **T.E. Karlsson:** None.

Poster

502. Impacts of Sleep Disruption

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Program #/Poster #: 502.14/V7

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 1R15GM122058-01

Title: Sleep duration influences the amount and clearance of stress granules in *Caenorhabditis elegans*

Authors: *M. K. DOUGHERTY, C. SAUL, L. CARMAN, M. D. NELSON, J. C. TUDOR; Biol., St. Joseph's Univ., Philadelphia, PA

Abstract: Stress granules are non-membrane bound aggregates of messenger ribonucleoproteins that are biomarkers of cellular stress. It has been shown in cells *in vitro* that suppression of the mammalian target of rapamycin (mTOR) pathway and its non-mammalian orthologue target of rapamycin (TOR) is associated with an increase in stress granule formation. It has also been shown that the mTOR pathway is suppressed in response to sleep deprivation in mice. Despite the possible connection via the TOR/mTOR pathway, there has not been any previous evidence linking sleep deprivation with stress granule formation. Our present investigation uses the nematode *Caenorhabditis elegans* to model how stress granule formation and clearance are modified by sleep duration. *C. elegans* experience two different types of sleep: developmentally-timed sleep, which occurs between the different larval stages of the worm, and stress-induced sleep, which occurs in response to a stressor such as heat shock. These different types of sleep are mediated by distinct mechanisms and there are known mutants and genetic manipulations that produce either sleep deprived or sleep enhanced animals for each type of sleep. Through employing these techniques and genetic crosses, we developed novel strains of *C. elegans* that model each type of sleep deprivation or enhancement and have RFP-labeled PAB-1 protein, a key component of stress granules. In addition to modifying sleep duration via genetic means, we also sleep deprived wildtype fluorescently labeled animals using mechanical disturbances.

Animals genetically deprived of developmentally-timed sleep appear to have more stress granules in the middle of their sleep period than the sleeping wildtype. Animals with enhanced stress-induced sleep have stress granules that are smaller in size and cleared faster than wildtype, while sleep deprived animals have granules that are slower to clear. Animals that were manually deprived of stress-induced sleep were similarly slower to clear stress granules. This work explores novel mechanisms, such as stress granules, by which sleep deprivation affects the flow of genetic information inside cells.

Disclosures: **M.K. Dougherty:** None. **C. Saul:** None. **L. Carman:** None. **M.D. Nelson:** None. **J.C. Tudor:** None.

Poster

502. Impacts of Sleep Disruption

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Program #/Poster #: 502.15/V8

Topic: F.08. Biological Rhythms and Sleep

Support: KAKENHI 15K18966
KAKENHI 18K14811
KAKENHI 19H03142
KAKENHI 17H06095

Title: Where does the dreamless mutation take effect?: Generation of NALCN-FLEx and NALCN-flox knock-in mice

Authors: *T. FUJIYAMA[1], S. MIZUNO[2], M. ABE[3], S. KANNO[1], M. KAKIZAKI[1], K. IWASAKI[1], A. IKKYU[1], N. HOTTA-HIRASHIMA[1], M. YAMADA[1], C. MIYOSHI[1], M. SATO[1], T. KANDA[1], K. SAKIMURA[3], S. TAKAHASHI[2], H. FUNATO[1], M. YANAGISAWA[1];
[1]Yanagisawa / Funato Lab., WPI-IIIS, The Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; [2]Lab. Animal Resource Center, Univ. of Tsukuba, Tsukuba, Ibaraki, Japan; [3]Brain Res. Institute, Niigata Univ., Niigata, Japan

Abstract: Although sleep is a ubiquitous animal behavior, the molecular/neural basis mechanism of REM sleep (REMS) remains unknown. We performed high-throughput screening of ENU-mutagenized mice in order to identify genes regulating sleep/wake behavior, and established the *Dreamless* mutant pedigree shows about 50% reduction in 24-h REMS time. We identified a nucleotide change specific to *Dreamless* mutant mice within the exon9 in *Nalcn* gene. The single nucleotide substitution leads to a single amino acid substitution (N315K) of the gene product leak cation channel NALCN that we termed *Dreamless*. We adopted CRISPR/Cas system to recapitulate *Dreamless* phenotype, then confirmed that the one base substitution was responsible

for REMS abnormality, suggesting that the identified gene is related to the regulation of daily REMS time. To elucidate the molecular/neural basis of REMS regulation by NALCN, we utilized genome editing tools and generated genetically-modified *Nalcn* mutant bearing flox and FLEx (flip and excision) knock-in mice for loss-of and gain-of-function studies, respectively. In *Nalcn-FLEx* mice, we observed that the mice with a systemic Cre-expressing line *Actb-iCre* showed the *Dreamless*-like phenotype on the electroencephalogram and electromyogram (EEG/EMG) analysis. On the other hand, in *Nalcn-flox* mice, we confirmed the neuronal subtype-specific deletion of *Nalcn* mRNA expression in adult brain tissue. Now we are planning to analyze sleep and wakefulness by using these two *Nalcn* gene mutant mouse lines.

Disclosures: **T. Fujiyama:** None. **S. Mizuno:** None. **M. Abe:** None. **S. Kanno:** None. **M. Kakizaki:** None. **K. Iwasaki:** None. **A. Ikkyu:** None. **N. Hotta-Hirashima:** None. **M. Yamada:** None. **C. Miyoshi:** None. **M. Sato:** None. **T. Kanda:** None. **K. Sakimura:** None. **S. Takahashi:** None. **H. Funato:** None. **M. Yanagisawa:** None.

Poster

502. Impacts of Sleep Disruption

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Program #/Poster #: 502.16/V9

Topic: F.08. Biological Rhythms and Sleep

Support: CONACyT Fellow 374823
UdG PROSNI 2016-2018 RGC
CONACyT No. PN 2016-01-465

Title: Melatonin modifies SOX2+ cell proliferation in dentate gyrus and modulates SIRT1 and MECP2 in long-term sleep-deprivation

Authors: *A. HINOJOSA GODINEZ[1], G. LOPEZ-ARMAS[2], M. E. FLORES SOTO[3], L. JAVE-SÚAREZ[4], M. LUQUÍN DE ANDA[1], A. GÁLVEZ CONTRERAS[1], I. RUSANOVA[5], O. P. GONZALEZ-PÉREZ[6], R. E. GONZALEZ-CASTAÑEDA[1];
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Abstract: Melatonin is a pleiotropic molecule that, after a short-term sleep deprivation, promotes the proliferation of neural stem cells in the adult hippocampus. However, this effect has not been observed in long-term sleep deprivation. The precise mechanism exerted by melatonin on the modulation of neural stem cells is not entirely elucidated, but evidence indicates that epigenetic regulators may be involved in this process. In this study, we investigated

the effect of melatonin treatment during a 96-h sleep-deprivation and analyzed the expression of epigenetic modulators predicted by computational text mining and keyword clusterization. Our results showed that the administration of melatonin under sleep-deprived conditions increased the MeCP2 expression and reduced the SIRT1 expression in the dentate gyrus. We observed that Let-7b, miR-132, and miR-124 were highly expressed in the dentate gyrus after melatonin administration, but they were not modified by sleep-deprivation. In addition, we found more Sox2+/BrdU+ cells in the subgranular zone of the sleep-deprived group treated with melatonin than the untreated group. These findings may support the notion that melatonin modifies the expression of epigenetic mediators that, in turn, regulate the proliferation of neural progenitors in the adult dentate gyrus under long-term sleep-deprived conditions.

Disclosures: A. Hinojosa Godinez: None. **R.E. Gonzalez-Castañeda:** A. Employment/Salary (full or part-time):; Universidad de Guadalajara. 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.; CONACyT. **G. Lopez-Armas:** None. **L. Jave-Súarez:** None. **M.E. Flores Soto:** None. **M. Luquín de Anda:** None. **O.P. Gonzalez-Pérez:** None. **A. Gálvez Contreras:** None. **I. Rusanova:** None.

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.17/V10

Topic: F.08. Biological Rhythms and Sleep

Support: NIH HL 123331
NIH HL124576
NIH AG054104

Title: Sleepstate modulation in calcium transients in CAMKII CA1 hippocampal neurons in APP knock-in mice varies with genotype

Authors: P. V. FENIK[1], C. LIU[2], K. PULLUM[1], ***S. C. VEASEY**[1];
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Abstract: Introduction: We find that chronic short sleep induces hippocampal neural injury. Hippocampal (HC) calcium/calmodulin kinase II (CAMKII) neurons are some of the most vulnerable neurons in Alzheimer's disease. We hypothesized that calcium transient frequencies in HC CAMKII neurons increase in active wakefulness and that CSS may further perturb CAMKII neuron calcium homeostasis, thereby contributing to CSS injury to the HC.
Methods: Amyloid precursor knock-in mice with the NL or NL+G+F mutations (3 mos, male

and female) were stereotaxically-injected with AAV5 GCamp6f into HC, then implanted with a Grin lens to focus on HC CAMKII neurons and later a baseplate for *in vivo* microscopy. Baseline sleep/wake recordings were obtained at 9 mos. The frequency of single neuron calcium transients in discrete neurons (50-150/mouse) was analyzed across active wake (exploratory AW), quiet wake (in nest head up, QW), behavioral sleep (S).
Results: Significant sleep state and genotype differences in transient rates were observed. Specifically, NL mice showed baseline calcium transient frequencies for AW, QW and S of 1.3±0.09, 0.5±0.07 and 0.15±0.03 bursts/minute. Although periods of behavioral phasic rapid-eye-movement (REM) sleep (ear and whisker twitches with postural atonia) were quite brief, calcium transients increased with apparent phasic REM sleep. AW rates were higher than in QW ($t=8.5$, $p<0001$) and S ($t=12.0$, $p<0.0001$), and QW was greater than S ($t=3.8$, $p<0.001$). In NLGF mice, behavioral state differences were also observed for AW vs QW ($p<0.01$), AW vs S ($p<0.0001$), but were of lesser magnitude, 0.5±0.03; 0.3±0.03; 0.2±0.02 for the two genotypes, and the AW transient frequency in NLGF mice was far less than in NL mice ($t=8.0$, $p<0.001$), while not different across strains for QW or S. Two findings specific to NLGF mice were synchronous and prolonged fluorescence of 5-9 adjacent cells firing during AW or upon arousal, and far higher αf/fx for NLGF mice was far higher than for NL mice, despite lower transient rates, $p<0.001$.
Conclusion: Active exploratory wakefulness increases calcium transients significantly and may thereby perturb metabolic homeostasis in CA1 CAMKII neurons. NLGF mice, at an age when plaques and memory impairments are seen, show greater calcium αf/fx in AW, despite lower transient frequencies, supporting the concept that wake-induced calcium perturbation may contribute to CAMKII neuron vulnerability.

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Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: BBSRC BB/S015922/1

Title: Synchronisation of UP-state termination during SWS is driven by thalamic inputs onto L1 interneurons

Authors: *Y. HAY, T. FUCHSBERGER, A.-L. KOERLING, T. QUARRELL, O. PAULSEN; Univ. of Cambridge, Cambridge, United Kingdom

Abstract: The neocortex is composed of excitatory and inhibitory neurons that are massively interconnected, allowing for the generation of sustained pattern of activity. During slow-wave sleep, anaesthesia, and quiet wakefulness, neuronal network is synchronised and fluctuates between periods of high synaptic activity (UP-states) and periods of relative quiescence (DOWN-states). UP-states may terminate spontaneously by synaptic depression and/or build-up of activity-dependent potassium conductances. It has been proposed that GABAB receptors (GABABRs) activation contributes to the increase of activity-dependent potassium conductance and thus would promote the termination of UP-states. Furthermore, neurogliaform interneurons (NGFCs), a class of Layer 1 (L1) GABAergic interneurons, have been shown to activate post-synaptic GABABRs located on the dendritic tree of L2/3-L5 pyramidal neurons. This induces a long-lasting hyperpolarization of pyramidal distal dendritic tree that reduces the neuronal excitability. We propose that activation of L1 NGFCs promotes UP-state termination. Finally, higher-order thalamic nuclei strikingly project to L1 of most cortical areas and could thus have a major effect in the synchronisation of UP-state termination. Our results show that higher-order thalamic neurons preferentially target L1 NGFCs and indirectly activate GABABR-mediated conductances in L2/3 pyramidal neurons. We suggest that higher-order thalamic nuclei activation could mediate the synchronous termination of UP-states throughout cortical areas during slow-wave sleep.

Disclosures: Y. Hay: None. **T. Fuchsberger:** None. **A. Koerling:** None. **O. Paulsen:** None. **T. Quarrell:** None.

Poster

502. Impacts of Sleep Disruption

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NIH R01 MH039683
NIH R01 NS069777
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Title: Control of wakefulness and cortical electrical activity by basal forebrain Lhx6 and Npas1 neurons in the mouse

Authors: *C. YANG[1], J. T. MCKENNA[1], J. M. MCNALLY[1], M. ANDERSON-CHERNISHOF[1], S. WINSTON[1], S. CHAN[2], R. E. BROWN[1];
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Abstract: The basal forebrain (BF), an important brain region for regulating sleep-wake, attention and reward processing, contains a large and diverse population of GABAergic neurons. However, the physiological role of different GABAergic subpopulations is still unclear due to the limitations of existing markers for identification. Here, we investigated two strains of mice expressing Cre Recombinase and a fluorescent marker under the control of transcription factors active in areas of the developing brain which generate forebrain GABAergic neurons, as well as in adults: Lim-homeobox 6 (Lhx6) and neuronal PAS domain 1 (Npas1). Immunohistochemical staining revealed that Lhx6+ neurons represented a mixed population, including many of the parvalbumin (PV+) neurons which we previously showed promote cortical gamma activity (Kim et al., 2015), and a subset of cholinergic neurons. In contrast, Npas1+ neurons were not PV+ or cholinergic. Using a chemogenetic approach combined with conventional frontal cortex electroencephalogram (EEG)/neck muscle electromyogram (EMG) recordings, we examined alterations of sleep patterns and cortical activity by bilaterally exciting the BF Lhx6+ and Npas1+ neurons. CNO (0.3 mg/kg) alone had no significant effect on sleep-wake behavior or cortical EEG in mice without transduction of BF neurons, when compared to vehicle (saline) injections (N=4). Chemogenetic activation of BF Lhx6+ neurons significantly increased wakefulness after IP injection of CNO as compared to IP injection of vehicle (wake percentage within 1.5h after IP injection, CNO vs. vehicle: 82.0±5.2% vs 42.8±4.6%, N=7, p=0.0011, paired-t-test), accompanied with an immediate increase in frontal cortical gamma band power (14.4±5.3% increase within 30min after IP injection, N=7, p=0.0313, Wilcoxon matched-pairs signed rank test) and an increase in locomotor activity (59.7±7.1% increase within 30min after IP injection, N=3). Chemogenetic activation of BF Npas1+ neurons even more strongly increased wakefulness (wake percentage within 1.5h after IP injection, CNO vs. vehicle: 93.5±6.5% vs 33.3±3.6%, N=2). However, the gamma band power during wakefulness or locomotor activity were not markedly altered. Our data indicate that Lhx6+ neurons, generated in the medial ganglionic eminence and implicated in neuropsychiatric disorders, include BF PV neurons and other BF neurons which promote wakefulness, cortical gamma activity and locomotor activity. Npas1+ neurons represent a novel subtype of BF wakefulness-promoting neurons.

Disclosures: C. Yang: 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. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Merck MISP. **J.M. McNally:** None. **M. Anderson-Chernishof:** None. **S. Winston:** None. **S. Chan:** None. **R.E. Brown:** None.

Poster

502. Impacts of Sleep Disruption

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Program #/Poster #: 502.20/V13

Topic: F.08. Biological Rhythms and Sleep

Support: PRODEP MAMG- DSA/103.5/16/7722

Title: The effect of prenatal sleep chronodisruption on metabolism of rat progeny

Authors: *A. E. SÁNCHEZ-GARCÍA[1], K. A. MARCIANO DIMAS, JR[2], M. BARRADAS-VAJONERO[3], C. PERALTA VÁZQUEZ[3], A. G. MENDOZA[2], K. V. SOSA-HUERTA[3], A. OLIVERAS-HERNANDEZ[3], T. CIBRIAN-LLANDERAL[4], R. AYALA-MORENO[6], M. A. MELGAREJO-GUTIERREZ[5];
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Abstract: In order to keep the homeostasis, certain hormones are usually released at certain moments of the day. By altering the sleep, it is altered the circadian rhythm, so the metabolic pathways that function the best with this system, start to be dysregulated. This can lead to non communicable chronic diseases, that includes obesity, insulin resistance, hypertension and dyslipidemia. It's been reported that the deprivation of sleep during the pregnancy produce a higher blood pressure in the rat's offspring.The alteration given the chronodisruption in animal models could lead to morphological changes in organs such as the kidneys and pancreas. The aim of the present study was to investigate the effect of sleep chronodisruption on the metabolic components of offspring rats. All experiments were conducted in accordance with the NOM-1997 for the Care and Use of Animals. For this purpose, were used female rats were paired with 4 male rats. The experimental rats were maintained in a disrupted light cycle (each 4h) with lights on at 0700 h and lights off 1100 h in a first day pregnancy . The control group were manteined to a 12L:12D light cycle with lights on at 0700 h . At birth were sacrificed 2 pups by rat/group to obtain serum for samples to measure glucose, insulin, cholesterol, triglycerides, leptin and grelin. The weight and long were measured as well, and the time of the development for the audition and vision senses were reported, taking as reference the separation of their ears from the head and the openness of the eyes. Preliminary results showed that there were no statistically ($P>0.05$) difference between the number of the breeding. Although one experimental group has shown lower weight and long and has been the smaller (10 pups), the other experimental group showed more consistent weights and had the bigger offspring (13 pups). The measurements of this later group is similar to the control groups. The results of the glucose,

insulin, cholesterol, triglycerides, ghrelin and leptin are still in hold.
Financial resource: PRODEP MAMG- DSA/103.5/16/7722

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Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: NRF-2018H1A2A1063084

Title: Voltage-gated potassium channel shaker promotes sleep via thermosensitive GABA transmission

Authors: *J.-H. KIM, Y. KI, H. LEE, M. HUR, J.-H. HUR, C. LIM;
UNIST, Ulsan, Korea, Republic of

Abstract: Genes and neural circuits coordinately regulate sleep homeostasis. However, it remains elusive how these endogenous factors shape animal sleep in response to environmental changes. Here, we found that *Shaker* (*Sh*)-expressing GABAergic neurons projecting onto dorsal fan-shaped body (dFSB) constitute a neural pathway important for temperature-adaptive sleep behaviors in *Drosophila*. Loss of *Sh* function potently suppressed sleep at low temperature whereas light and high temperature cooperatively gated *Sh* effects on sleep. RNA interference-mediated depletion of *Sh* expression in GABAergic neurons partially phenocopied *Sh* mutants. Moreover, trans-heterozygous mutations that decrease GABA transmission rescued *Sh* mutant sleep. Transgenic mapping further revealed that the ionotropic GABA receptor, *Resistant to dieldrin* (*Rdl*), in dFSB neurons acts downstream of *Sh* and antagonizes the sleep-promoting effects of *Sh*. In fact, *Rdl* inhibited the intracellular cAMP signaling of constitutively active dopaminergic synapses on dFSB neurons at low temperature. On the other hand, high temperature silenced GABAergic synapses onto dFSB neurons, thereby potentiating the wake-promoting dopamine transmission. We propose that temperature-dependent switching between these two synaptic transmission modalities may adaptively tune the neural property of dFSB neurons to temperature shifts and reorganize sleep architecture for the benefit of animal fitness.

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Poster

502. Impacts of Sleep Disruption

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Support: WSU Postdoctoral Alcohol and Drug Abuse Research Program grant
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Title: Diurnal fluctuations of perineuronal nets in the rat medial prefrontal cortex

Authors: *J. H. HARKNESS[1], P. N. BUSHANA[2], E. T. JORGENSEN[5], A. E. GONZALEZ[3], D. M. HEGARTY[7], S. A. AICHER[8], T. E. BROWN[6], J. P. WISOR[2], B. A. SORG[4];
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Abstract: Extracellular matrix aggregations called perineuronal nets (PNNs) surrounding synapses of fast-spiking, parvalbumin (PV) -containing GABAergic interneurons and are important for stabilization of synapses following learning and for limiting plasticity after the critical period. Additionally, PNNs provide oxidative buffering capacity for PV cells. Chondroitin sulfates, which make up the majority of PNNs, provide substrates for oxidation/reduction reactions, thus acting as a source of protection against oxidative stress. Oxidative stress increases in the brain during periods of wakefulness, and is alleviated by sleep. We have previously shown that PNN intensity fluctuates with memory, experience, and drug exposure. Here, we investigated whether PNN intensity (measured by *Wisteria floribunda* agglutinin, WFA) also fluctuated throughout the diurnal and sleep/wake cycles and whether diurnal fluctuation also occurred in the AMPA/NMDA ratio in PV+/WFA+ cells in the medial prefrontal cortex (mPFC). PNNs, oxidative stress (8-oxo-dG), and PV intensity were quantified in the mPFC at four time points (ZT0, ZT6, ZT12, & ZT18) during the diurnal cycle. PNN intensity was decreased at ZT6 compared to ZT0, and increased at ZT12 and ZT18. PV intensity was also increased at ZT18 compared to ZT0. 8-oxo-dG intensity was decreased at all time points compared to ZT0. AMPA/NMDA ratios were increased ($p = 0.06$) at ZT18 compared to ZT0. Pilot studies show that excitatory (vGlut1) but not inhibitory (GAD65/67) puncta surrounding PV+/WFA+ cells are elevated at ZT18 vs. at ZT6. These data indicate that PNN,

PV, and oxidative stress intensity fluctuate throughout the sleep/wake cycle, with increases in PV and PNNs during the most active phase and oxidative stress marker lowest after maximal sleep. Additionally, the AMPA/NMDA ratio appears to follow fluctuations in PNN intensity. These findings suggest that diurnal fluctuations in PNN intensity could be important to other effects of PNNs on learning, memory, and behavior.

Disclosures: **J.H. Harkness:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Rewire Neuroscience. **P.N. Bushana:** None. **E.T. Jorgensen:** None. **A.E. Gonzalez:** None. **D.M. Hegarty:** None. **S.A. Aicher:** None. **T.E. Brown:** None. **J.P. Wisor:** None. **B.A. Sorg:** None.

Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: F32 AG056081-03
Howard Hughes Medical Institute

Title: Nitrogen metabolism regulates sleep homeostasis

Authors: ***J. L. BEDONT**[1], A. KOLESNICK[1], D. MALIK[1], M. DAVIDOV[1], A. WELJIE[1], A. SEHGAL[2];
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Abstract: It is increasingly appreciated that metabolism and sleep are heavily coupled, with recent studies demonstrating associations of sleep homeostasis with lipid processing and carbohydrate metabolism, among many other biochemical pathways. However, many of these studies have been descriptive, leaving the causal relationships underlying even most known metabolite / sleep correlations poorly understood. We attempted to assess what metabolic pathways might be centrally important regulators or effectors of sleep homeostasis by conducting mass spectroscopy on heads from a panel of several severely sleep-deficient Drosophila melanogaster mutants. The most consistently affected pathways included acyl-carnitine synthesis and, interestingly, a wholesale remodeling of nitrogen metabolism. Ammonia equivalents in the form of arginine or ornithine can be transformed into less toxic forms suitable for excretion or re-use by over half a dozen different biochemical pathways. These equivalents seem to be funneled into the specific branch identified in our mass spectroscopy screen by transcript-level changes in enzyme expression in the sleep mutants. We have also found, through RNAi and dietary supplementation experiments, that manipulation of this pathway is sufficient to regulate sleep

amount and consolidation. This may be due to modulation of neurotransmitter levels downstream of the nitrogen processing network. We are actively testing whether this same pathway has similar cause-effect relationships during more acute perturbations of sleep. Ultimately, these studies have important implications for understanding physiological sleep homeostasis, and perhaps even for pathological changes such as neurodegeneration that have been associated with chronic perturbations of sleep.

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Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: NIH: HL084207
NIH: HL127673

Title: Metabolic regulation of sleep: The role of lateral hypothalamic leptin circuit

Authors: *U. SINGH[1], B. A. TOTH[1], K. C. DAVIS[1], K. SAITO[1], J. JIANG[1], G. F. BUCHANAN[2], H. CUI[1];
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Abstract: Adequate body energy store and sufficient sleep are essential for health, and any disruptions in these physiological processes can lead to serious health consequences including obesity, diabetes, and cardiovascular diseases. Literature support an intimate association between sleep and energy balance - short sleep duration and poor sleep quality are associated with weight gain and obesity, whereas obesity has been identified as an independent risk factor for poor sleep quality and excessive daytime sleepiness. Despite this bidirectional, feedforward, pernicious association between obesity and sleep disorders, the neural substrates underlying this association remain poorly understood. Adipocyte-derived metabolic hormone, leptin, exhibits diurnal rhythm in circulation and regulates energy balance and rhythmic expression of behaviors such as sleep and daily locomotor activity, yet the underlying neural circuits mediating these effects are unclear. Here we show that leptin acts on a subset of lateral hypothalamic area (LHA) GABAergic neurons to affect sleep and energy balance. Selective deletion of leptin receptor (LepR) in the LHA of adult mice resulted in increased body fat gain, decreased locomotor activity, frequent sleep onset and increased sleep time especially in subjective day, resembling excessive daytime sleepiness in human. Chemogenetic activation of this subpopulation of LHA GABAergic neurons completely disrupts sleep and dramatically increases exploratory locomotor

activity. These findings identify the LHA as a critical site where circulating metabolic hormone leptin acts to affect sleep and provide a possible explanation why severely obese patients who are commonly associated with leptin resistance often experience poor sleep quality and excessive daytime sleepiness.

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Poster

502. Impacts of Sleep Disruption

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Program #/Poster #: 502.25/V18

Topic: F.08. Biological Rhythms and Sleep

Support: NIMH 60670

Title: Typical and atypical spindles found in rapid eye movement sleep

Authors: *C. GONZALEZ[1], K. SWIFT[3], K. KEUS[1], G. R. POE[2];
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Abstract: Sleep spindles are short bursts (0.5-2s) of high frequency (11-15 Hz) electrical activity in the cerebral cortex and hippocampus that have been directly linked with the formation and consolidation (or "storing") of memories across multiple species. They are produced by activity in two connecting regions of the brain: the thalamus and the cortex. The cortex is the final destination of stored memories and is associated with higher cognitive functions. Sleep spindles have long been a hallmark of non-rapid eye movement (NREM) sleep, and their possible presence in rapid-eye movement (REM) sleep has been distinctly ignored. While a handful of studies have identified the presence of REM sleep spindles, a thoroughly descriptive study of such phenomenon is necessary. **We predict these REM spindles will behave in a manner that is distinct from their NREM counterparts.** We utilized EEG recordings in the medial prefrontal cortex, the parietal cortex, and CA1 of the hippocampus during sleep in rats and identified the presence of two phenomena atypical to REM sleep: the presence of spindles in a typical 10-15 Hz range as well as waxing and waning spindle-like behavior in the 5-9 Hz theta range. We analyzed for spindle density and length in these three areas, as well as power spectral data. We also analyzed the occurrence of these phenomena across the female estrous cycle. In addition, in the coming months we will use the novel object placement task to look for behavioral markers and impacts on memory. These data will be the first to rigorously characterize, define, and examine the presence of these typical and atypical REM spindles.

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Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: NIMH Grant #60670
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Title: Sleep facilitates insight into temporal hidden patterns

Authors: *R. S. GUTHRIE[1], K. KEUS[2], C. GONZALEZ[3], J. YANO[1], J. HOLLOWAY[4], K. CLARK[5], M. A. GLUCK[6], I. LERNER[7], B. A. GROSS[8], G. R. POE[8];
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Abstract: Findings reported in human studies indicate that sleep facilitates insight. One proposed view suggests that ***key elements in the environment necessary for insight are already encoded in part during waking, then replayed during sleep, allowing the pieces to self-assemble into insight***. Further, a novel computational hypothesis called *temporal scaffolding* suggests that sleep-dependent insight is more likely to occur when requiring the detection of hidden temporal patterns. Here, we tested this hypothesis by developing a novel task for rodents that measures whether sleep facilitates insight into a hidden temporal rule. Animals were exposed to a track with three sequential choice points where the first and second were forced choices and at the final point animals chose freely the left, center, or right path. Animals needed to choose the same path as the first forced choice to receive a reward. Thus they needed to learn a hidden temporal rule. Five sequence trials were given in each session with 3 hours of sleep or sleep deprivation occurring between sessions, all on the same day. We found that rats who slept for 3 hours between sessions improved their ratio of correct sequence choices from random to nonrandom, demonstrating the sleep period facilitated a gain of "insight" into the hidden temporal rule. The performance of those deprived of sleep over the same period remained static. This study demonstrates the feasibility of insight-like tasks in rodent models and may facilitate future work using in-vitro electrophysiological techniques to study replay.

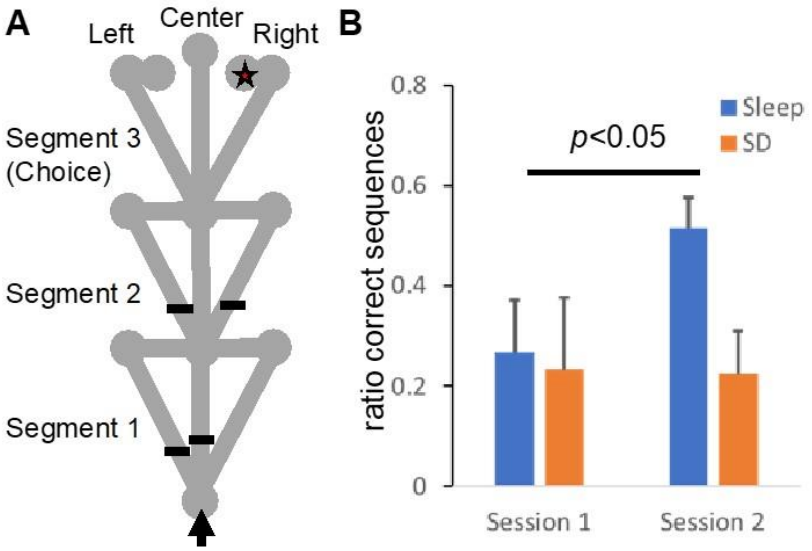

Figure 1. A) Insight track layout from above. Arrow indicates the starting point of all trials. Black lines indicate blocked paths. In this case the rat was forced to go Right in segment 1, Center in segment 2, then only rewarded (rad star) when choosing Right for segment 3. Five sequence trials were given in each session with 3 hours of sleep or sleep deprivation occurring between sessions, all on the same day. **B**) Ratio of correct to total performed sequences on the sequential choice insight task before (Session 1) vs. after (Session 2) sleep (n=6) or sleep deprivation (SD, n=4).

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Poster

502. Impacts of Sleep Disruption

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Topic: F.08. Biological Rhythms and Sleep

Support: NIMH 60670
Department of Integrative Biology and Physiology

Title: Early not delayed propranolol injection enhances fear extinction recall after trauma exposure in rats

Authors: J. A. HOLLOWAY, Y. CABRERA, B. A. GROSS, *G. R. POE;
Integrative Biol. and Physiol., UCLA, Los Angeles, CA

Abstract: Sleep disturbance is a significant underlying factor in the development of maladaptive responses to emotionally traumatic events. Heightened sympathetic nervous system activity is a hallmark of post-traumatic stress disorder (PTSD), and sleep is known to be an important regulator of both emotion and autonomic nervous system function. Recent studies from our lab and other groups show that changes in sleep after traumatic stress exposure can predict PTSD symptomatology. We have also found that an activity increase in the sympathetic locus coeruleus during sleep causes the same sleep changes as trauma-exposed animals who display PTSD symptoms. The locus coeruleus fires at all times except throughout REM sleep and for seconds prior to each sleep spindle in non-REM sleep. Thus, noradrenergic receptors are occupied except during these times. Beta adrenergic receptors enhance long term potentiation and prevent its reversal, depotentiation. Depotentiation is necessary for the consolidation of reversal learning including the extinction of fear that allows resilience after trauma. We hypothesize that continuous activity in the noradrenergic locus coeruleus during sleep leads to PTSD by preventing the depotentiation-dependent consolidation of extinction (e.g. safety) contexts. We tested whether the intervention of blocking beta noradrenergic receptors during sleep after extinction training, using propranolol (40 mg/kg) would confer resilience to trauma-exposed animals. As the critical window for memory consolidation is 4-5 hours after learning, we delayed propranolol injection in a control group by 5 hours. We found that immediate post-extinction propranolol enhanced fear extinction recall, reducing freezing to levels shown in non-trauma-exposed animals, whereas later propranolol injection impaired extinction memory such that freezing levels were similar to those of untreated trauma-exposed animals. Thus, blockade of noradrenergic pathways in the immediate period following extinction training enhances extinction memory consolidation in trauma-exposed groups, presumably by supporting sleep-dependent depotentiation of fear circuits which requires low noradrenergic tone.

Disclosures: J.A. Holloway: None. **Y. Cabrera:** None. **B.A. Gross:** None. **G.R. Poe:** None.

Poster

502. Impacts of Sleep Disruption

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 502.28/V21

Topic: F.08. Biological Rhythms and Sleep

Support: MH60670

Title: Post-stress sleep features in gonadally intact females affect fear learning

Authors: *Y. CABRERA[1], J. HOLLOWAY[1], J. JIMENEZ[1], K. SWIFT[3], G. R. POE[2]; [2]Dept. of Integrative Biol. and Physiol., [1]UCLA, Los Angeles, CA; [3]Mol. and Integrative Physiol., Univ. of Michigan, Ann Arbor, MI

Abstract: Sleep is essential in the memory consolidation process. Specific sleep stages are characterized by patterns of neural activity that facilitate strengthening, weakening, and reorganization of memory networks. Rapid eye movement (REM) sleep is important in the consolidation of emotional memories like fear conditioning and extinction. Recently, we showed the importance of locus coeruleus (LC) silence during REM sleep to support proper reversal learning in males. As the LC is the primary producer of norepinephrine (NE) in the cortex, LC silence signifies a pause in NE and its long-term potentiation enhancing effects, allowing flexible modification of memory synapses via depotentiation processes. Malfunctions in this system or conditions of high stress could contribute to excess NE release during REM sleep, increasing susceptibility to fear memory processing disorders. Since there are well known sex differences in prevalence of anxiety and fear memory disorders like PTSD, we explored whether sleep after stress differs in high hormone vs. low hormone stage female rats. The major estrous cycle hormones, estrogen and progesterone, modulate mood, cognition, and autonomic nervous system, and receptors for these hormones are known to be present in memory- and stress-related regions like the hippocampus, amygdala, and the LC. These may directly affect sleep-dependent memory processes and contribute to deficits in adaptive fear learning (i.e. poor extinction recall). Rats were implanted with probes to determine sleep/wake state and identify electrophysiological activity patterns congruent with memory processes. Upon examination of baseline sleep architecture, we found that REM sleep is selectively suppressed in females during the dark phase of proestrus, and that spectral power in the theta range (5-9 Hz), the predominant oscillatory frequency in REM sleep, also increases in the high hormone phases. Analysis of post-stress exposure sleep showed fragmentation of REM sleep bouts and decreased theta spectral power in REM, particularly in the low hormone phases, and these were linked to poorer extinction recall. Thus, estrous cycle effects on sleep affect fear memory consolidation processes, and may increase vulnerability to fear disorders.

Disclosures: Y. Cabrera: None. **J. Holloway:** None. **J. Jimenez:** None. **K. Swift:** None. **G.R. Poe:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.01/V22

Topic: F.08. Biological Rhythms and Sleep

Support: NIGMS/NIH IDeA Award P20GM103449

Title: Changes in neuronal synchrony alter slow wave activity across infraslow cycles

Authors: *M. B. DASH, **A. GREEN**;
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Abstract: Slow wave activity (SWA; the EEG power between 0.5 and 4 Hz during non-rapid eye movement sleep), is the best electrophysiological marker of sleep need. Given the apparent importance of this patterned neuronal activity for sleep function, it is critical to understand the physiological mechanisms that regulate the expression of SWA. In male Sprague-Dawley rats, we observed that SWA exhibits pronounced variability across infraslow timescales (~40 - 120s periods). Infraslow fluctuations in SWA were coordinated across the cortex and characterized by distinct alterations to individual slow waves (i.e. increased slope, amplitude, and duration and a concomitant reduction in the total number of waves and proportion of multipeak waves were associated with peaks in infraslow SWA). To investigate the physiological underpinnings of infraslow SWA, we used a freely available dataset comprised of extracellular unit recordings during consolidated NREM episodes in male Long-Evans rats. We observe that infraslow SWA was associated with alterations in neuronal synchrony surrounding "On"/"Off" periods and changes in the number and duration of "Off" periods. By contrast, changes in the firing rates of either excitatory or inhibitory neurons within the cortex were not associated with infraslow SWA. Together, these observations characterize a novel regulatory mechanism of SWA and highlight that SWA expression is regulated across shorter timescales in addition to its well-characterized homeostatic decline. With the ability to modulate SWA throughout the cortex, infraslow fluctuations may contribute to sleep function by coordinating local and global expressions of SWA.

Disclosures: M.B. Dash: None. **A. Green:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.02/V23

Topic: F.08. Biological Rhythms and Sleep

Support: VA Merit (I01BX002661)

Title: Chemogenetic activation of melanin concentrating hormone neurons attenuates sleep disturbances and contextual conditioning in predator odor trauma mouse model of PTSD

Authors: S. KUMAR[1], R. SHARMA[2], P. SAHOTA[3], *M. M. THAKKAR[1];
[1]Neurol., HSTMV Hospital/University of Missouri, Columbia, MO; [2]Truman VA Med. Center/University of Missouri, Columbia, MO; [3]Neurol., Univ. of Missouri, Columbia, MO

Abstract: BACKGROUND: Insomnia and associated sleep disturbances are amongst severe and persistent symptoms observed in individuals with post-traumatic stress disorder (PTSD). In fact, insomnia is believed to maintain and/or exacerbate PTSD symptoms. Effective treatment to attenuate sleep disturbances may accelerate recovery however; current medications are

ineffective. We have recently reported that mice exposed to predator odor trauma (POT) display contextual conditioning along with severe and protracted insomnia. Since melanin-concentrating hormone (MCH) is implicated in sleep regulation, we hypothesized that chemogenetic activation of MCH neurons will attenuate sleep disturbance and normalizes sleep. To test our hypothesis, we performed contextual conditioning, with predator odor (soiled cat litter) as the unconditional stimulus (US), contextual cage as the conditional stimulus (CS) and examined the effects of chemogenetic activation of MCH neurons on contextual conditioning and sleep. **METHODS:** Transgenic MCH-cre mice (expressing Cre-recombinase under MCH promoter control) were used as our animal model. Standard surgical protocol was used to perform bilateral infusion of excitatory DREADD (AAV/hSyn-DIO-hM3Dq-mCherry; 600nL/side) in MCH rich lateral hypothalamus followed by unilateral implantation of wire electrodes to record hippocampal field potentials. **Day 1:** Memory acquisition was performed by replacing the recording cage of MCH-cre mice with CS and allowing them to explore for 30 minutes followed by exposure to US for 90 minutes. On completion, CS were replaced with respective recording cages. **Day 2:** MCH neurons were activated by systemic (intraperitoneal) infusion of clozapine-N-oxide (CNO, 5 mg/Kg; CNO group) or saline (Controls) just before light (sleep) onset. **Day 3:** Memory recall testing was performed by exposing the mice to contextual cages (without US) for 120 min. On completion, mice were euthanized; brain removed and processed for immunofluorescence to quantify MCH neurons with DREADD expression. **RESULTS:** DREADD induced activation of MCH neurons resulted in a significant reduction in wakefulness with a concomitant increase in NREM sleep during light period on Day 2. Furthermore, during memory recall testing, while the controls displayed electrophysiological indicators of traumatic memories including increase in hippocampal theta and gamma activities along with increased wakefulness, no such effects were observed in the CNO group. **CONCLUSION:** Our results suggest that chemogenetic activation of MCH neurons attenuates sleep disorders and contextual conditioning in the predator odor trauma, mouse model of PTSD.

Disclosures: **M.M. Thakkar:** None. **R. Sharma:** None. **P. Sahota:** None. **S. Kumar:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.03/V24

Topic: F.08. Biological Rhythms and Sleep

Support: Russian Foundation for Basic Research, #18-04-01252

Title: Neuronal activity of brainstem reticular formation neurons across the sleep-wake cycle in the domestic chicken

Authors: *O. LYAMIN[1,2], A. BAKHCHINA[2,3], I. SHAMSIEV[2,4], J. SIEGEL[1];
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Abstract: In contrast to mammals, rapid eye movement (REM) sleep or paradoxical sleep (PS) in most bird species lasts only 5-10 seconds when scored based on conventional polygraphic criteria (cortical arousal, muscle tone reduction and rapid eye movements). The neuronal activity, which underlies REM sleep has never been recorded in birds. The aim of this study was to examine neuronal discharge of the brainstem neurons in the domestic chicken *(Gallus gallus domesticus)* during the sleep-wake cycle to better understand the nature of REM sleep in birds. EEG, neck electromyogram, electrooculogram and single neuron activity were recorded in 5 freely-moving domestic chickens (4-5 mo old) across the sleep-wake cycle. Twenty one of the recorded neurons were located in the area of midbrain reticular formation and 16 neurons in the pontine reticular formation. The unit activity (average and instantaneous discharge rate) was analyzed in 4-sec epochs. Fifteen out of 37 neurons (41% of the recorded cells) had higher firing rates both in waking and REM sleep when compared to non-REM sleep or slow wave sleep (W+R+ cells). Among them, 9 neurons (24%) discharged during REM sleep with a greater rate than during active wakefulness (AW) (W+R++ cells). Additional 8 neurons (22%) selectively increased the firing rate in REM sleep while their discharge rate in AW, quiet wakefulness and non-REM sleep was low (0.01-1.20 Hz; R+ cells). Only two cells (5%) were classified as “max-active” in AW when compared to other states (W+ cells). Twelve cells (32%) were classified as state indifferent (less than 50% change across sleep waking states). Therefore, based on the profile of the discharge of reticular neurons, the described cell types in the chicken are similar to that in mammals (cats, rats and mice). Rapid eye movements is the key parameter, which unambiguously indicates REM sleep in the chicken. At the same time, the degree of cortical EEG arousal and muscle tone reduction (the hallmark of REM sleep / PS in mammals) during REM sleep in the chicken is greatly variable as also described in other bird species. Thus, we have found that up to 35 % of episodes of REM sleep in different chickens were recorded during EEG slow waves showing some similarity with the data previously reported in the echidna, platypus and in the ostrich. Our neuronal and polygraphic data supports the idea that REM sleep in the chicken may occur at the level of brainstem (midbrain and pontine reticular formation) without cortical activation and that this may be the case in other birds.

Disclosures: O. Lyamin: None. **A. Bakhchina:** None. **I. Shamsiev:** None. **J. Siegel:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.04/V25

Topic: F.08. Biological Rhythms and Sleep

Support: Diversity Supplement NS90994

Title: MiR-190 acts in the pupal nervous system to affect the arousal system and sleep behavior in *Drosophila melanogaster*

Authors: *E. J. RIVERA-RODRÍGUEZ[1], M. HOBIN[2], P. CHEN[2], L. C. GRIFFITH[2];
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Abstract: Sleep is a widely conserved behavior, known to influence many cognitive and physiological functions. Studies have implicated microRNAs in the regulation of gene expression changes that control sleep behavior. The Griffith lab screened a library of 141 microRNA sponges using the fruit fly *Drosophila melanogaster*, in order to find microRNAs involved in sleep regulation (Goodwin et al., 2018). This screen showed miR-190 to be involved in the regulation of sleep. Flies expressing the miR-190 sponge (*miR-190SP)* in a pan-neuronal manner showed decreased and fragmented sleep, as well as changes in other sleep parameters. Expressing *miR-190SP* in a limited number of cells in different brain regions by means of the *Gal4/UAS* system showed that disruption of miR-190 function must occur in a large number of neurons to affect *Drosophila* sleep regulation. At the molecular level, RNA sequencing of adult heads showed that pan-neuronal expression of *miR-190SP* induces an up or downregulation of multiple genes, among those, 9 genes which are intimately involved in dopamine (DA) signaling, the major pro-arousal system of the fly. Feeding flies pan-neuronally expressing the miR-190 sponge a low dose of the tyrosine hydroxylase inhibitor 3IY rescues their sleep phenotype, causing an increase in total sleep without significant effects on control animals. Temporally limiting expression of *miR-190SP* to early larval or adult stages does not affect sleep. Pan-neuronal-pupal inhibition of miR-190, however, results in a significant decrease in sleep, phenocopying the results obtained by expressing the miR-190 sponge throughout development. This suggests that miR-190 acts to establish adult sleep behavior during the pupal stage. Taken together, our results suggest that miR-190 acts during development to specify the activity of the adult arousal system and adult sleep behavior.

Disclosures: E.J. Rivera-Rodríguez: None. **M. Hobin:** None. **P. Chen:** None. **L.C. Griffith:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.05/V26

Topic: F.08. Biological Rhythms and Sleep

Support: Iowa Center for Research by Undergraduates (ICRU) Fellowship
Beth L. Tross Epilepsy Professorship

Title: Examination of a role for the locus coeruleus in CO_2-induced arousal from sleep

Authors: *C. J. HAUSER[1], A. L. ZOCHER[1], G. F. BUCHANAN[2,3];
[1]Heath and Human Physiol., Univ. of Iowa, Iowa City, IA; [2]Neurol., Carver Col. of Medicine, Univ. of Iowa, Iowa City, IA; [3]Iowa Neurosci. Inst., Iowa City, IA

Abstract: CO_2-induced arousal is a critical protective mechanism. Under normal conditions, if the airway is occluded, arterial partial pressure of CO_2 ($PaCO_2$) rises. This can happen repeatedly during sleep, in conditions like obstructive sleep apnea. The elevated $PaCO_2$ acts as a powerful arousal stimulus. Once awake, airway tone increases thereby correcting the obstruction, allowing breathing to resume, and returning $PaCO_2$ to baseline. Impaired CO_2-induced arousal may contribute to multiple fatal conditions during sleep such as sudden infant death syndrome (SIDS) and sudden unexpected death in epilepsy (SUDEP). In these conditions, individuals do not arouse in response to increased $PaCO_2$ resulting in acidosis and eventual death. Mechanisms of CO_2-induced arousal from sleep are not well understood. Determining these mechanisms may provide insight to the pathophysiology underlying these conditions and lead to the development of preventive therapies. Previous research has shown that dorsal raphe nucleus (DRN) serotonergic (5-HT) neurons and external lateral parabrachial calcitonin gene-related peptide expressing neurons ($PBel^{CGRP}$) are necessary for CO_2-induced arousal. These structures are interconnected with the locus coeruleus (LC), which also plays a role in regulating arousal through its extensive noradrenergic (NA) projections to wake-promoting regions such as the cortex and thalamus. Here we tested the hypothesis that the NA neurons in the LC are involved in CO_2-induced arousal. Adult, male and female, C57BL/6J mice were treated with DSP-4 (50 mg/kg, *i.p.;* two injections, seven days apart), a neurotoxin selective to LC NA neurons, or saline. Mice were implanted with epidural EEG and nuchal EMG electrodes, allowed to recover, and habituated to the gas chamber. During non-rapid eye movement (NREM) sleep, mice were exposed to 7% CO_2 (CO_2; in 21% O_2 and balance N_2) or room air (RA; 21% O_2 and balance N_2) and arousal latency was recorded. All trials were performed within the first six hours of the light phase. DSP-4-treated mice exhibited no significant difference in arousal latency to CO_2 or RA (3.461 ± 0.455 min vs. 2.493 ± 0.564 min; $p = 0.104$; $n = 6$). Control mice exhibited normal, robust CO_2 responsiveness during sleep with a significant reduction in arousal latency to CO_2 compared to RA (1.074 ± 0.071 min vs. 3.347 ± 0.652 min; $p = 0.017$; $n = 6$). This finding of decreased CO_2 responsiveness during sleep upon partial LC NA neuronal destruction suggests a role for the LC in CO_2-induced arousal. Further research into the extent of this role and the signaling pathways between these implicated structures is warranted.

Disclosures: C.J. Hauser: None. **A.L. Zocher:** None. **G.F. Buchanan:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.06/V27

Topic: F.08. Biological Rhythms and Sleep

Title: Frequency-dependent modulation of sleep and wakefulness via optogenetic stimulation of the basal forebrain parvalbumin neurons

Authors: *J. HEO, J. LEE, C. KIM, T. KIM;
Dept. of Biomed. Sci. and Engin., Gwangju Inst. of Sci. and Technol., Gwangju, Korea, Republic of

Abstract: The basal forebrain (BF) parvalbumin (PV) neurons have been known for controlling sleep and wakefulness. Optogenetic stimulation of BF PV neuron in mice regulates the gamma band oscillations in the cortex via corticopetal projection, and also induces arousal state, supporting the wake-promoting property of BF PV neurons. Interestingly, BF PV neurons also project to TRN of which intermittent stimulation at 8 Hz generates sleep spindles and protects NREM sleep. Indeed, our preliminary results from unilateral optogenetic stimulation of the BF PV neurons at 8 Hz showed a slight increase in NREM sleep. However, the function of this anatomical connection in sleep-wake control is still unclear. Therefore, we sought to investigate the effects of bilateral BF PV neuron stimulation to confirm the frequency-dependent bidirectional modulation of sleep and wakefulness. For selective stimulation of the BF PV neurons, we stereotaxically injected double-floxed ChR2-eYFP viral vector (AAV5-DIO-ChR2-e YFP) into PV-Cre transgenic mice (strain 012358, Jackson Lab) of BF region bilaterally (AP=0, ML=1.6 and -1.6, V=-5.5 from the bregma). After 2weeks electrodes for EEG were implanted on the frontal and parietal lobe of the left hemisphere and optical fiber (200μm, 0.22 NA) in BF region of both hemispheres. Laser light was generated from 473nm Blue DPSS laser driver. The light was delivered via fiber-optic cable connected to fiber optic cannula. The baseline EEG of 24-hour sleep-wake behaviors was recorded, followed by 6-hour EEG recordings including 2-hour optogenetic stimulation with intermittent 8Hz (from ZT06 to ZT08) and tonic 40Hz (from ZT18 to ZT20) stimulation protocols. We compared the evoked gamma power between unilateral and bilateral stimulation by giving 40Hz optical stimulation and analyzed sleep-wake behaviors after manual scoring. Bilateral hemisphere evoked gamma power was stronger than unilateral counterpart (bilateral to ipsilateral ratio 1.46 in the frontal EEG). We are expecting that intermittent stimulation at 8 Hz of the bilateral BF PV neurons will increase NREM sleep during stimulation and post-stimulation periods, and the bilateral stimulation at 40Hz will also decrease NREM like our previous preliminary data with a stronger effect than that of the unilateral stimulation. The final results are pending. We found that the increment of NREM sleep by intermittent stimulation of bilateral BF PV neurons at 8 Hz and the decrement of

NREM by 40 Hz were more clearly validated with bilateral stimulation of BF PV neurons. It may suggest that the BF PV neurons have a dual function of sleep- and wake-promotion depending on the rate and mode of neuronal firings of them.

Disclosures: **J. Heo:** None. **J. Lee:** None. **C. Kim:** None. **T. Kim:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.07/V28

Topic: F.08. Biological Rhythms and Sleep

Support: NARSAD/NIMHD 2G12MD007592
NIH/NIMH R21 R21MH109953
NIH 2T34GM008048

Title: Scully in sleep regulation and dementia

Authors: *A. ARZOLA, Jr, P. SABANDAL, K.-A. HAN;
Biol. Sci., Univ. of Texas at El Paso, El Paso, TX

Abstract: Sleep is an important physiological process for memory, metabolic waste clearance in the brain, and other cognitive functions. The fruit fly *Drosophila melanogaster* and humans share aging-associated sleep features including reduced sleep time and fragmented sleep architecture. Sleep dysfunction is a common feature of Alzheimer's disease and related dementia; however, the mechanism by which sleep dysfunction contributes to dementia is not well understood. We found that the *scully* mutant flies have abnormal sleep. Scully is the fly homolog of 17-β-hydroxysteroid dehydrogenase 10 (HSD17β10), a versatile mitochondrial enzyme known to bind amyloid β-peptide and is overexpressed in the brain of Alzheimer's disease patients. Interestingly, *scully* mutant flies show the features of dementia that include dysfunctional inhibitory control and memory loss. To investigate whether abnormal sleep in *scully* is linked to dementia, we are investigating whether reinstatement of normal sleep in *scully* would rescue the dementia phenotypes and whether overexpressed *scully* causes sleep anomaly or dementia or both. The progress of the study will be presented. This study may provide novel insights in the role of *scully* in Alzheimer's disease and related dementia.

Disclosures: **A. Arzola:** None. **P. Sabandal:** None. **K. Han:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.08/V29

Topic: F.08. Biological Rhythms and Sleep

Support: NIH grant R01-NS078410

Title: Sex differences in active-phase sleep amount are partially driven by X chromosome dosage

Authors: *I. S. N. NICHOLS, S. ANDERSON, H. HRNCIR, Z. HERNANDEZ, A. P. ARNOLD, K. N. PAUL;
Integrative Biol. and Physiol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Sex differences in total sleep amount in mammals are largely dependent on gonadal hormones. However, there are a number of sex differences in sleep traits that are not driven by gonadal hormones. The most prominent of those are total sleep amount during the active phase and sleep amount/intensity during recovery from sleep loss. Female mice consistently exhibit less sleep amount during the active phase, and less sleep amount and intensity during recovery from sleep loss than males. We have previously shown that these effects are related to sex chromosome complement. The current study sought to determine if the effects of the sex chromosomes are due to X chromosome dosage (total number of chromosomes), or the presence of the Y chromosome. This experiment takes advantage of a mouse line that alters the dosage effects of sex chromosomes and sex-linked genes. The XY star line (denoted as XY*) is comprised of four sex chromosome complement phenotypes: XO (phenotypic female), XX (phenotypic female), XXY (phenotypic male), XY* (phenotypic male). This mouse line allows the investigation of: 1) dosage effects of the X chromosomes, and 2) the presence or absence of the Y chromosome. This mouse line also serves as a model for Turner Syndrome and Klinefelter syndrome. Adult mice were implanted with four stainless steel electroencephalograph (EEG) and electromyography (EMG) recording electrodes. Mice were subjected to 24 hrs of baseline (spontaneous) sleep-wake recording. Following baseline, mice were subjected to six hrs of sleep deprivation via a gentle handling procedure (starting at the onset of the light phase) and allowed to recover during the remainder of the 24-hr recording period. X dosage had an effect on active-phase baseline sleep amount, but no effects during recovery from sleep loss. Repeated measures ANOVA revealed an interaction between phase and genotype ($F_{3,8}$= 8.956, p=.006). XY mice had more sleep than XO mice (p=0.030) and slightly, but not significantly, more sleep than XX mice (p=.051). XXY mice were not different from any other groups. These results suggests that the ability of the Y chromosome to influence sleep in mice is dependent on X dosage. These

results also suggest that the ability of sex-linked genes to influence sleep is independent of phenotypic sex.

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Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.09/V30

Topic: F.08. Biological Rhythms and Sleep

Support: NIH grant R01-NS078410

Title: Time restricted feeding (TRF) improves sleep in a mouse model of Huntington's disease

Authors: Y. TAHARA[1], S. ANDERSON[2], *I. S. NICHOLS[2], C. A. GHIANI[3], ***K. N. PAUL**[2], C. S. COLWELL[4];
[2]Integrative Biol. and Physiol., [3]Pathology, [4]Psychiatry and Biobehavioral Sci., [1]Univ. of California Los Angeles, Los Angeles, CA

Abstract: Disturbances in the daily sleep-wake cycle are a common feature experienced by individuals with neurodegenerative disorders. Huntington's disease (HD) is the most common genetically determined neurodegenerative disease. Patients with HD exhibit a variety of sleep abnormalities that include difficulty initiating sleep at bedtime, and more frequent nighttime arousals. Mouse models of HD exhibit similar sleep deficits. Using a mouse model of HD that expresses the human mutation (BACHD), we have successfully improved behavioral and autonomic deficits using a time restricted feeding (TRF) protocol that limits the daily food intake into a 6-hr window during the animal's active phase. In this study, we sought to determine whether TRF was sufficient to improve sleep-wake phenotypes in the BACHD mouse. Adult male mice were anesthetized and implanted with electroencephalograph (EEG) and electromyograph (EMG) electrodes for the 24-hr recording of sleep and wake states. Multivariate ANOVA revealed that during baseline recording of spontaneous sleep and wake states, BACHD mice exhibited more total wakefulness ($p=.034$) than wild-types (WT). TRF dramatically improved the temporal pattern of sleep behavior. The BACHD mice on TRF spent more time sleeping during the day compared to untreated BACHD mice ($p=.026$). However, the overall amount of total sleep over 24 hrs. was not altered. These effects of TRF were more prominent in BACHD mice than WTs. To our knowledge, this is the first demonstration that TRF can improve sleep parameters in a mouse model of HD. A critical gap in our knowledge is whether TRF specifically alters the temporal pattern of sleep stages, sleep homeostasis, or cortical up/down states that reflect slow wave activity.

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Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.10/V31

Topic: F.08. Biological Rhythms and Sleep

Support: R01NS103422

Title: Transcriptomic analysis of sleep states

Authors: ***A. KULKARNI**[1], T. BJORNESS[2], A. SUZUKI[2], G. KONOPKA[1], R. GREENE[2]; [1]Neurosci., [2]Psychiatry, Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: Sleep deprivation has detrimental effects on a wide array of biological processes. A leading, yet controversial proposal for sleep function is a weakening and/or pruning of synaptic connections and net decrease in synaptic strength that can aid in metabolic homeostasis and memory. It is possible that both strengthening and weakening processes can occur during sleep. Neuronal activity and gene expression during sleep or in response to the loss of sleep can provide a window to the enigma of sleep function. Sleep-loss is associated with characteristic rebound and resolution of slow wave sleep - slow wave activity (SWS-SWA), and an increase in pyramidal cell mini-frequency and amplitude, reflecting changes in synaptic strength, that recover with recovery sleep (RS). Here, we examine the gene expression landscape in response to sleep deprivation and recovery sleep against ad-lib sleep in mouse frontal cortex as this region is associated with highest intensity of slow wave activity during slow wave sleep and shows greatest change in SWS-SWA in response to loss of sleep. We observed a sleep-loss induced differential gene expression of almost one half of the expressed frontal cortical transcriptome. Genes shared by both sleep-loss and RS with significantly increased expression suggests roles in lipid mobilization for energy utilized during protein metabolism as well as involvement in neuropsychiatric disorders such as cognitive deficits, Parkinson disease and epilepsy. Consistent with reduction in synaptic strength during sleep, shared genes with significantly reduced expression across sleep-loss and RS suggests their contribution in controlling synaptic strength and connection to neurological diseases such as, autism spectrum disorders intellectual disability, mental retardation, etc. Together, these findings facilitate the molecular underpinning of the sleep function and contribute to the better understanding of pathways leading to detrimental effects of sleep deprivation.

Disclosures: **A. Kulkarni:** None. **T. Bjorness:** None. **A. Suzuki:** None. **G. Konopka:** None. **R. Greene:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.11/V32

Topic: F.08. Biological Rhythms and Sleep

Title: Hippocampal population activity during REM and slow wave sleep

Authors: *M. A. F. FRAZER[1], G. R. POE[2];
[1]Univ. of California Los Angeles, Los Angeles, CA; [2]Dept. of Integrative Biol. and Physiol., UCLA, Los Angeles, CA

Abstract: The necessity of sleep to learning and memory processing is well-established. The specific mechanisms that facilitate memory consolidation during each stage of sleep, however, are still an area of active investigation. To explore further the underlying mechanisms of sleep, we have used *in vivo* calcium imaging in freely-behaving mice to record from hippocampal CA1 cells across sleep stages. We have found that each sleep stage demonstrates unique population activity, likely underlying each stage's role in sleep-dependent memory consolidation.

Disclosures: M.A.F. Frazer: None. **G.R. Poe:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.12/V33

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant 60670
Rackham Graduate School

Title: Sex differences in the electrophysiological makeup of sleep in gonadally intact rats

Authors: *K. KEUS[1], K. SWIFT[6], C. GONZALEZ[2], Y. CABRERA[3], J. JIMENEZ[4], J. HOLLOWAY[4], B. C. CLAWSON[7], B. A. GROSS[5], G. R. POE[5];
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Physiol., UCLA, Los Angeles, CA; [6]Mol. and Integrative Physiol. Dept., [7]Molecular, Cellular, and Developmental Biol. Dept, Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: There are marked differences in the makeup of sleep in both males and females, with some studies indicating that sleep is undeniably altered by the menstrual cycle in women. However, not much is known about the electrophysiological makeup of sleep in gonadally intact female rodents. Using electroencephalographic (EEG) activity, we show that the estrous cycle alters sleep states and features in multiple cortical areas and the hippocampus in males and free-cycling females. Namely, we found that, compared with males and other phases of the estrous cycle, time spent awake increases during proestrus, sacrificing time spent in non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. As a result, the estrus phase showed rebound in sleep architecture with increases in REM and NREM. Further, spectral power also fluctuates in accordance with the estrous cycle. Proestrus shows increased delta (0.5-4 Hz) and gamma (30-60 Hz) power, where as REM theta (5-9 Hz) increased during both proestrus and estrus compared to other phases. Proestrus also showed an increase in slow wave activity (SWA) and cortical sleep spindle density during NREM, and increases in interregional NREM and REM spectral coherence. This data demonstrates the wide impact of the estrous cycle on sleep, providing the foundation for future research to use gonadally intact male and female rats during sleep studies.

Disclosures: K. Keus: None. **K. Swift:** None. **C. Gonzalez:** None. **Y. Cabrera:** None. **J. Jimenez:** None. **J. Holloway:** None. **B.C. Clawson:** None. **B.A. Gross:** None. **G.R. Poe:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.13/V34

Topic: F.08. Biological Rhythms and Sleep

Support: NIH Grant GM088156
NIH Grant HL07953

Title: Evidence for a role of tachykinin-1-expressing preoptic area neurons in isoflurane-induced unconsciousness

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Abstract: Though anesthetics have been used in the medical field for over 150 years and are currently used in over 300 million surgeries annually, the precise mechanisms by which this diverse category of drugs produces a state of unconsciousness are not fully understood.

Similarities between anesthetic-induced unconsciousness and the state of non-rapid eye movement (NREM) sleep has led to the hypothesis that anesthetics produce unconsciousness in part through the endogenous pathways that regulate sleep and arousal. Previous work has shown that isoflurane, a volatile anesthetic, activates sleep-promoting neurons (SPNs) in the ventrolateral preoptic area (VLPO) as well as the supraoptic nucleus (SON). Additionally, manipulations of either of these SPN populations affect the response to isoflurane anesthesia, further suggesting that SPNs in the POA may mediate isoflurane-induced unconsciousness. However, the VLPO and SON are not the only POA regions known to contain SPNs, and it is unclear whether isoflurane also activates SPNs across the broader POA. Labeling SPNs in this region has proved challenging due to a lack of unique markers capable of identifying them within the highly heterogeneous POA. However, recent work has shown that tachykinin-1 (Tac1) expressing neurons in the POA promote NREM sleep when activated, and thus provide a reliable marker for SPNs throughout the POA. Given the evidence in VLPO and SON, we hypothesized that activation of POA SPNs is involved in producing isoflurane-induced unconsciousness. Using loss of righting reflex as a proxy for unconsciousness, induction and emergence dose-response curves for isoflurane were measured in adult Tac1-Cre mice before and after a lesion or sham lesion of Tac1 POA neurons. Tac1 POA neurons were lesioned using bilateral stereotaxic injections of a virus encoding a Cre-dependent diphtheria toxin A subunit, while controls received injections of a Cre-dependent mCherry fluorescent protein. Post-lesion, we observed a rightward shift of the entire dose-response curve, with the EC_{50}, or dose at which 50% of the population had lost the righting reflex, shifting from 0.73% (95% CI: 0.71%-0.76%) isoflurane at baseline to 0.85% (95% CI: 0.80%-0.89%) at 3 weeks post-injection. Sham lesioned animals showed a leftward shift of the curve, with the EC_{50} shifting from 0.72% (95% CI: 0.69%-0.76%) to 0.57% (95% CI: 0.55%-0.60%) isoflurane. Interestingly, no significant effects were detected in the emergence dose-response curve. These results suggest the intriguing possibility that Tac1 POA neurons play a role in the induction of isoflurane-induced unconsciousness, but not in emergence from the anesthetic state.

Disclosures: **S.L. Reitz:** None. **M.B. Kelz:** None.

Poster

503. Sleep Regulation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 503.14/V35

Topic: F.04. Stress and the Brain

Support: NIMH Silvio Conte Center 1P50MH094271
JPB Foundation
Canadian Institute for Advanced Research
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Title: Coupled sleep, attention and dopamine receptor deficits after early life stress

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Abstract: Early life adversity results in a variety of neural and behavioral deficits later in life. Particularly, sleep regulation and attentional function are susceptible to early life stress (ELS), leading to insomnia and inattentive behavior. However, the association between sleep and attentional deficits after ELS as well as its molecular basis remains largely unknown. Here, we employed the fragmented maternal care model (Rice et al. 2008) in mice to investigate the influence of ELS on later sleep and attention as well as the underlying molecular changes. In adult (>P90) male mice, sleep regulation (-7% NREM, +8% wake duration; $p<0.05$ vs control care), prefrontal gamma oscillation during waking (+13% relative power with aberrant peaks; $p<0.05$) and attentional function (-11% correct on a touchscreen 2-choice visual task; $p<0.05$ vs control care) were disrupted after fragmented maternal care between postnatal days P2-P9. Acute experimental sleep deprivation (4-hour gentle handling) led to comparable attentional reduction in normally-reared adult mice (-12% correct; $p<0.01$ vs baseline), while no further attentional reduction by acute sleep deprivation was observed in mice after early life fragmented care. This suggests that persistent, poor sleep signatures caused by ELS might underlie their attentional impairment in adulthood. At a molecular level, both fragmented care and acute sleep deprivation induced a parallel increase of dopamine D2 receptors and decrease of D4 receptors in the adult anterior cingulate cortex (ACC), which correlated with attentional performance. Thus, altered dopamine signaling in the ACC caused by insufficient sleep might be a basis for attentional impairment. Strikingly, neither sleep impairment, altered gamma oscillation nor ACC dopaminergic changes were observed in female mice after fragmented care, revealing unanticipated gender differences in the susceptibility to ELS for these particular physiological measures. Our findings reproduce in mice the insomnia and inattentiveness in humans after early adversity and offer a mechanistic association between them, which is potentially mediated by altered D2/D4 dopaminergic transmission in the ACC.

Disclosures: Y. Makino: None. **K. Osada:** None. **T.K. Hensch:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.01/V36

Topic: G.01. Appetitive and Aversive Learning

Support: China MOST 2012YQ03026005
China MOST 2013ZX0950910
China MOST 2015BAI08B02
NNSFC 91432114
NNSFC 91632302
Beijing Municipal Government

Title: Basolateral amygdala projecting anterior cingulate cortex neurons control reward devaluation

Authors: *Z. YUAN, Z. QI, Y. CUI, Q. FENG, M. LUO;
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Abstract: The incentive value of food is not only determined by its physical characteristics, but also by the homeostatic state of animals. For instance, water is a strong reward for thirsty, rather than water-satiated, animals; sucrose, a natural reward stimulus, can become less attractive as the intake volume increases. These phenomena could be referred to as reward devaluation. Disorder in reward devaluation may result in obesity or anorexia, even drug addiction. Here, we show that anterior cingulate cortex (ACC) is involved in the process of reward devaluation. First, fiber photometry revealed that CaMKII positive neurons in ACC were silenced when mice were either drinking voluntarily or receiving water passively, and the inhibition strength was gradually weakened with increased water intake. Furthermore, lesion or inhibition of ACC neurons slowed the devaluation process and gave rise to over-intake of reward (water). In contrast, activation of ACC neurons accelerated reward devaluation and led mice to consuming less reward. In addition, we found that basolateral amygdala (BLA) projecting ACC neurons underlie this effect. In conclusion, BLA-projecting ACC neurons contribute substantially to bidirectional regulation of reward intake by modulating its devaluation process.

Disclosures: Z. Yuan: None. **Z. Qi:** None. **Y. Cui:** None. **Q. Feng:** None. **M. Luo:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.02/V37

Topic: G.01. Appetitive and Aversive Learning

Support: NSERC Discovery Project RGPIN-2019-06947

Title: Increased noradrenergic activity within the basolateral amygdala enhances appetitive extinction

Authors: *L. H. CORBIT;
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Abstract: Noradrenergic signaling has been shown to facilitate extinction in both appetitive and aversive conditioning paradigms. Converging evidence also suggests that the basolateral amygdala (BLA) is part of the neural circuitry that underlies extinction, and may play a role in the noradrenergic modulation of extinction memory. This study investigated effects of manipulating noradrenergic activity within the BLA on the long-term expression of extinction of stimulus-reward associations. Rats surgically implanted with cannulae aimed at the BLA were trained to lever-press for food reward in the presence of three discriminative stimuli. Responding was then extinguished over two consecutive days. Prior to the third extinction session, rats received intra-BLA infusions of either saline, noradrenaline (NA), or a specific NA agonist (clenbuterol) or antagonist (propranolol). Spontaneous recovery of responding was assessed four weeks later. We found that treatment with NA or the beta-2-receptor agonist clenbuterol enhanced, whereas blockade of beta-adrenergic receptors with the antagonist propranolol impaired extinction learning evidenced by changes in spontaneous recovery compared to a saline control. These results demonstrate that manipulations that increase noradrenergic activity in the BLA increase the long-term efficacy of extinction of appetitive learning.

Disclosures: L.H. Corbit: None.

Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.03/V38

Topic: G.01. Appetitive and Aversive Learning

Support: McKnight Memory and Cognitive Disorders Award
NARSAD Young Investigator Grant
R01DA043533

Title: Role of basolateral amygdala to nucleus accumbens projections in mediating flexibility of sign- and goal-tracking rats

Authors: *D. E. KOCHLI, S. E. KEEFER, U. GYAWALI, D. J. CALU;
Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: The psychological and neurobiological mechanisms underlying individual differences in addiction vulnerability require further investigation. A hallmark of addiction is behavioral inflexibility of drug use in the face of negative consequences. Previous studies suggest that even prior to drug experience, goal-tracking rats remain sensitive to changing outcome value, while

"addiction-vulnerable" sign-tracking rats demonstrate inflexible responding that does not reflect the current value of the outcome. The present work utilizes an outcome specific satiety devaluation in a Pavlovian lever autoshaping (PLA) procedure to test the hypothesis that sign-tracking rats rely on the basolateral amygdala (BLA) to nucleus accumbens (NAc) pathway to rigidly encode appetitive cue value that is insensitive to changes in outcome value. Using a chemogenetic disconnection design, we inactivate BLA-NAc pathway during outcome specific satiety devaluation and measure lever- and foodcup-directed behaviors in the PLA task. In this procedure, a brief lever insertion predicts non-contingent delivery of a food pellet reward. While no interaction with any stimulus is necessary, sign-trackers preferentially interact with lever predictive cues, whereas goal-trackers preferentially interact with the food cup. Intermediate rats interact with both the lever and food cup. Prior to non-reinforced PLA test sessions, all rats (mCherry, hM4Di-mCherry) received systemic clozapine (0.1 mg/kg) injections and were either sated on the training pellet (devalued condition) or homecage chow (valued condition). We conducted two non-sated PLA tests under non-reinforced or reinforced conditions. Data suggest BLA-NAc pathway supports lever-directed behavior for sign-tracking rats independent of outcome value (valued, devalued) and motivational state (sated, non-sated). Intermediate rats display increased behavioral flexibility when BLA-NAc pathway is inactivated, seemingly unmasking devaluation sensitivity in the intermediate rats that do not otherwise display differential responding to valued and devalued outcomes. This suggests appetitive cue value encoding in BLA-NAc may hinder expression of flexible behavior when outcome value changes. Goal-tracking rats' food cup responding is behaviorally sensitive to satiety devaluation and ongoing studies determine the extent to which activity in BLA-NAc mediates flexibility in goal-tracking rats. A more sophisticated understanding of the circuitry underlying individual differences in addiction vulnerability will inform translational efforts to improve addiction prevention, diagnosis and treatment.

Disclosures: D.E. Kochli: None. **S.E. Keefer:** None. **U. Gyawali:** None. **D.J. Calu:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

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Program #/Poster #: 504.04/V39

Topic: G.01. Appetitive and Aversive Learning

Support: NIDA R01 DA043533
McKnight Memory and Cognitive Disorders Award
NARSAD Young Investigator Grant #24950

Title: Role of basolateral amygdala to insular cortex projections in mediating individual and experience-dependent differences in flexibility of sign- and goal-tracking rats

Authors: *S. E. KEEFER, D. E. KOCHLI, S. Z. BACHARACH, D. J. CALU;
Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Recent studies have shown goal-tracking (GT) rats are sensitive to outcome devaluation while sign-tracking (ST) rats are not. With extended training, we observed GT rats display more ST responses, suggesting GT may become insensitive to devaluation with more training. To determine the effects of limited and extended training on devaluation sensitivity in GT and ST rats, we used a within subject satiety-induced outcome devaluation procedure. We sated rats on training pellets (devalued condition) or homecage chow (valued condition) prior to brief non-reinforced test sessions at limited (sessions 5/6) and extended training (after sessions 17/18) time points. Consistent with our prior study, after limited training, GT rats were sensitive to outcome devaluation, while ST rats were not. After extended training, GT rats remained sensitive to devaluation, while surprisingly, ST rats now showed devaluation sensitivity. The results confirm devaluation sensitivity is stable in GT rats and extended training unmasks flexibility in ST rats, suggesting distinct, potentially shifting neural mechanisms that decipher reward value. Because the basolateral amygdala (BLA) to anterior insular cortex (IC) pathway mediates devaluation, we sought to test the role of this pathway in mediating GT and ST differences in flexibility across training. We predicted after limited training, inactivating BLA-IC would abolish devaluation sensitivity in GT rats and not affect devaluation insensitivity of ST rats. After extended training, we predicted inactivating this pathway would block devaluation sensitivity in both GT and ST rats. We injected inhibitory DREADDs (hM4D-mcherry) or control (mCherry) virus bilaterally into the BLA and implanted bilateral cannulae into the IC for clozapine-*N*-oxide (CNO; 1mM, 0.25 µl/side) infusions to temporarily inactivate BLA terminals during devaluation tests. After limited training rats were sated on training pellets (devalued condition) or homecage chow (valued condition) and all rats received bilateral CNO infusions into the IC prior to brief non-reinforced test sessions. Preliminary results replicate devaluation sensitivity in control GT rats, while hM4D GT rats show blunted responding to both the devalued and valued conditions. Control and hM4D ST rats remained insensitive to devaluation after limited training. Ongoing studies are examining the effect of BLA-IC disconnection after extended training in GT and ST rats. These results demonstrate BLA-IC mediates behavioral flexibility and furthers our understanding of individual differences by recognizing behavioral and neural differences that relate to addiction vulnerability.

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Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.05/V40

Topic: G.01. Appetitive and Aversive Learning

Support: R01 DA035443

Title: A reciprocal cortical-amygdala circuit for the encoding and retrieval of detailed associative reward memories

Authors: *A. SIAS[1], A. K. MORSE[1], C. SHIEH[1], S. M. HOLLEY[2], V. GREENFIELD[3], C. CEPEDA[2], M. S. LEVINE[2,4], K. M. WASSUM[1,4];
[1]Dept of Psychology, [2]IDDRC, Semel Inst. for Neurosci. and Human Behavior, BRI, UCLA, Los Angeles, CA; [3]Dept of Psychology, UCLA, UCLA, CA; [4]Brain Res. Inst., UCLA, Los Angeles, CA

Abstract: Adaptive reward-related decision making requires anticipation of potential future rewarding events. This expectation is enabled by predictive environmental stimuli. These cues trigger the retrieval of often quite detailed memories of their associated rewards, which then inform adaptive reward pursuit and bias decision making. But very little is known of the neural circuits that mediate the encoding and subsequent retrieval of unique stimulus-reward associative memories. We addressed this gap in knowledge by combining optogenetics, chemogenetics, serial circuit disconnection, and a translationally-relevant behavioral task designed to assess the encoding and retrieval of detailed stimulus-reward memories. Using optical inhibition, we found basolateral amygdala (BLA) principle cells to be necessary for encoding detailed stimulus-reward memories. BLA inhibition upon reward delivery/consumption during Pavlovian stimulus-reward conditioning did not disrupt acquisition of a simple Pavlovian conditional approach response, but did prevent subjects from learning the unique stimulus-reward relationships, as evidenced by their inability to subsequently use such memories to guide choice behavior (Pavlovian-instrumental transfer) or adaptive conditional responding following outcome-specific devaluation. This result was replicated using optical inhibition of lateral orbitofrontal cortex (lOFC) terminals in the BLA, indicating lOFC-->BLA projections are critical for encoding stimulus-reward memories. Tract tracing revealed reciprocal connectivity between the BLA and lOFC and previously we showed that BLA-->lOFC, but not lOFC-->BLA projections are necessary for retrieving detailed stimulus-reward memories. Thus, we suspected that lOFCàBLA projections might enable the encoding of stimulus-outcome memories that are later retrieved via BLA-->lOFC projections. We found support for this hypothesis by multiplexing optogenetic and chemogenetic inhibition for a serial circuit disconnection. Collectively, these data reveal the lOFC-->BLA-->lOFC circuit to be essential for the encoding and retrieval of detailed stimulus-reward associative memories crucial for adaptive decision making.

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Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: G.01. Appetitive and Aversive Learning

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DP2 DK105570
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Smith Family Foundation Award
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Title: Midbrain dopaminergic input to basal amygdala gates state-dependent learning of salient cues

Authors: *A. LUTAS, H. KUCUKDERELI, O. ALTURKISTANI, C. CARTY, K. FERNANDO, A. U. SUGDEN, V. DIAZ, V. FLORES-MALDONADO, M. L. ANDERMANN; Beth Israel Deaconess Med. Ctr., Boston, MA

Abstract: The acquisition of responses in basal amygdala (BA) neurons to sensory stimuli that predict either salient appetitive or aversive outcomes is crucial for associative learning. We found that ventral tegmental area dopamine axons innervating BA ($VTA^{DA>BA}$) were activated by *both* rewards and punishments, and acquired responses to cues predicting these salient outcomes during learning. BA neurons downstream of these actions also acquired cue responses with learning, but separate populations represented reward-paired and punishment-paired cues. Following satiation, responses to reward cues in $VTA^{DA>BA}$ axons and BA neurons were attenuated, while responses to cues predicting aversive outcomes persisted or increased, indicating a shift in BA responses from reward related activity to threat related activity. We confirmed that dopamine levels increased in the BA during both reward and punishment predicting cues leading us to ask how this signal might control plasticity. Brain slice studies suggested that $VTA^{DA>BA}$ inputs may boost plasticity by increasing cAMP signaling across BA excitatory neurons, while restricting plasticity by enhancing lateral inhibition via BA interneurons. Preliminary *in vivo* imaging of cAMP in BA support this model of broad permissive plasticity during triggered by salient events. Through these actions, the same $VTA^{DA>BA}$ axons may provide a reinforcement signal of motivational salience that promotes learned responses to appetitive or aversive cues in distinct, intermingled sets of BA excitatory neurons.

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Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.07/V42

Topic: G.01. Appetitive and Aversive Learning

Support: SNF grant
Ambizione grant

Title: Hierarchical amygdala network dynamics reflect learning of adaptive behavioral patterns

Authors: ***Y. BITTERMAN**[1], J. COURTIN[1], J. GRÜNDEMANN[2], A. LÜTHI[1,3];
[1]Friedrich Miescher Inst. For Biomed. Res., Basel, Switzerland; [2]Dept. of Biomedicine, [3]Univ. of Basel, Basel, Switzerland

Abstract: Classically, the basolateral amygdala has been studied mainly in the framework of Pavlovian conditioning, leading to the identification of circuit elements that underlie stimulus related plasticity at the single-cell and neural-ensemble levels. However, we have only a rudimentary understanding of how learning of adaptive behavioral patterns relates to amygdala network dynamics. Using calcium imaging, we monitored with cellular resolution the activity of neuronal populations in the basolateral amygdala, as mice underwent partially-stochastic instrumental training that resulted in stereotypical, self-paced behavioral sequences. We used a data driven approach to identify structures in the dynamics of the population activity without additional behavioral or environmental information. The seemingly complex network activity was composed of simple latent dynamics that emerged consistently with learning, albeit variability in the neural representation of events across mice. Furthermore, the hierarchical structure of the network dynamics reflected the abstract structure of the learned behavioral patterns. Thus, latent dynamics provided a unified framework to study the relations between neural network activity and behavior, with testable predictions as to the system's susceptibility to specific behavioral and neuronal perturbations. Our results point to an amygdala function in driving state- and input- dependent behavioral patterns, with possible insights to amygdala maladaptive function in pathological conditions.

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Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.08/V43

Topic: G.01. Appetitive and Aversive Learning

Title: The effects of lesions of the amygdala and periaqueductal gray on learning from gains and losses

Authors: *C. A. TASWELL[1], V. D. COSTA[1], E. A. MURRAY[2], B. B. AVERBECK[2]; [1]Section on Learning and Decision Making, NIH/NIMH, Bethesda, MD; [2]NIMH/NIH, Bethesda, MD

Abstract: Adaptive behavior requires learning to gain rewards and avoid losses. Most work on learning has focused on learning to gain rewards. Therefore, we have developed a paradigm that allows us to examine whether the same or different neural systems underly learning from gains vs. losses. We have previously shown that Ventral Striatum plays a specific role in learning to select between rewarded outcomes (Taswell, C, et al, 2019). These results suggest that there is different neural circuitry that underlies learning from losses. Two areas of the brain that are good candidates and often thought to underlie different types of aversive learning are the amygdala and the periaqueductal gray. To assess whether one, both, or neither area is involved in learning from loss, we tested monkeys with lesions to the amygdala (n = 4) and monkeys with lesions to the periaqueductal gray (n = 4) on the same experiments used in the study above. We conditioned tokens as reinforcers in a task where animals could both gain and lose tokens. We ran four experiments; three used deterministic reinforcement and one used stochastic reinforcement. In all experiments, novel images were introduced at the beginning of blocks of about 100 trials, and the animals had to learn the gains or losses associated with each experiment. In the first deterministic experiment we introduced four images in each block which had associated outcomes of +2, +1,-1,-2 tokens. In the second experiment we added a cue with a value of 0 to the set (+2, +1, 0, -1, -2). In the third experiment mimicked the first, except 75% of the time, the outcome was the value of the cue, and 25% of the time, the outcome was 0. In the final experiment, -4 replaced -2 as the large token loss. The animals had to learn over trials, in each block, the outcomes associated with each cue, and choose the best cue in each trial. Our current results have found no deficits in learning for either group. However, the data for the monkeys with amygdala lesions shows some differences in actions typically associated with motivation. Specifically, monkeys with amygdala lesions take significantly more time to make choices (reaction time). In addition monkeys with amygdala lesions abort significantly more trials, which is a failure to make a choice after the options are presented.

Disclosures: **C.A. Taswell:** None. **V.D. Costa:** None. **E.A. Murray:** None. **B.B. Averbeck:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Program #/Poster #: 504.09/V44

Topic: G.01. Appetitive and Aversive Learning

Support: China MOST 2012YQ03026005
China MOST 2013ZX0950910
China MOST 2015BAI08B02
NNSFC 91432114
NNSFC 91632302
Beijing Municipal Government

Title: A brainstem circuit controlling the expression of natural and addiction memory

Authors: *R. LIN, J. LIANG, R. WANG, T. YAN, Z. GUO, Y. LIU, M. LUO;
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Abstract: Persistent memories of addiction drive drug cravings and relapse. By co-opting the dopamine (DA) population in the ventral tegmental area (VTA), addictive drugs—for example, opioids—induce excessive learning signals and the subsequent formation of drug-associated memories. However, little is known about whether the DA system is involved in the expression of memory under normal circumstances or in addiction. Here, we identify a unique midbrain DA population in the dorsal raphe (DRN) that is segregated from the canonical VTA DA population and functions as a critical component in controlling memory expression. Both rewarding and aversive stimuli activate DRN DA neurons in a learning-dependent manner, and the activity of these neurons is required for the expression of appetitive and fear memory. DRN DA neurons are also activated during the expression of opioid addiction memory, and ablation or inhibition of DRN DA neurons blocks the expression of memories that are associated with opioid seeking and withdrawal. Using the rabies screen, we found a glutamatergic input from an upstream brainstem area to DRN DA neurons that is enhanced by morphine administration. These upstream neurons show morphine-triggered increase in excitability, and silencing these neurons selectively impairs the expression of reward memories associated with opioids or foods while leaving the expression of aversive memories associated with opioid withdrawal or fear intact. These results pinpoint the essential functions of DRN DA neurons in regulating memory expression and highlight new targets for developing future addiction intervention strategies.
R.L. and J.L. contributed equally to this work.

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Poster

504. Appetitive and Incentive Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.10/V45

Topic: G.01. Appetitive and Aversive Learning

Title: Role of the cerebral ganglion in the shift of taste-preference by learning of *aplysia*

Authors: *N. TESHIMA[1], K. UMETA[1], Y. KATSUMATA[1], Y. YOSHIMI[1], T. NAGAHAMA[2];
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Abstract: Taste is an important sense to determine whether an intaken food should be ingested or rejected for survival. A marine gastropod *Aplysia* indicates clear taste preferences, which can be modified by experience and learning. For example, *Aplysia* prefers *Nori* extract but hates distilled water (DW). However, giving DW immediately after *Nori* extract makes *Aplysia* dislike *Nori* extract. In this work we attempted to reveal the role of cerebral ganglion in the taste-preference modification by the learning. Buccal mass and buccal ganglion and cerebral ganglion were isolated with retaining the connection with nerve bundles. The preparation was fixed under a microscope to observe the movement of the buccal mass responding to the administration of the Nori extract, DW or artificial sea water (ASW) to the radula. Only the administration of DW triggered the vigorous movement of the radula which probably indicates rejection of the tasting fluid. After the test sequential administrations of the *Nori* extract and distilled water to the buccal mass were repeated 20 times. After the sequential administration, the rejective movement of the buccal mass was observed responding to the administration of the *Nori* extract as well as the DW. The same experiments performed except for removing the cerebral ganglia. In this case, the rejective movement occurred responding to the administration of the DW but did not to the Nori extract even after the sequential administrations. Those results indicate that the learning by the sequential administration of the preferred and unpreferred tastes is processed by the cerebral ganglia in the preparation. The analysis of the neural network in the cerebral ganglion would clarify the mechanism of the learning. The imaging of cerebral ganglion sensitized with fluorescent serotonin-imprinted polymer nanoparticles were observed through microscope. Spike fluorescent changes indicating the serotonin secretion responding to each tastes were detected in the experiment. The serotonin-imaging may be potential tool for revealing the neural network for modification of the taste preference through the learning.

Disclosures: **N. Teshima:** None. **K. Umeta:** None. **Y. Katsumata:** None. **Y. Yoshimi:** None. **T. Nagahama:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 504.11/V46

Topic: G.01. Appetitive and Aversive Learning

Support: NIH grants AA024571
DA041674

Title: Characterization of prefrontal-subcortical circuitry in execution and inhibition of reward seeking behaviors

Authors: *J. P. CABALLERO, D. E. MOORMAN;
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Abstract: The rodent prelimbic cortex (PL) plays an important role in the learning and regulation of actions, including those directed to rewards. PL, however, is a heterogeneous region composed of neurons projecting to various areas throughout the brain, each of which play different roles in behavioral control. These different PL networks likely have diverging roles in the context of reward seeking, learning, and action control that have not yet been thoroughly elucidated. The goal of this research is to characterize the role of specific PL ensembles, defined by their projection targets, in the context of the learning, expression, and inhibition of reward seeking. Our focus is on PL neurons projecting to three areas receiving some of the most dense efferent projections: mediodorsal thalamus (MD), ventral striatum (VS), and lateral hypothalamus (LH). In these studies, male Long-Evans rats receive retrograde AAV in each PL target region to express cre recombinase in neurons projecting to that area. In the same surgery, rats receive a cre-dependent hM4Di inhibitory DREADD in the PL, thus producing selective hM4Di expression in PL neurons projecting to one of the three selected targets. Post-surgery, food and fluid-restricted rats are then trained on a fixed ratio 1 (FR1) sucrose seeking task and then tested in FR1 acquisition, FR1 expression, early extinction, late extinction, and cue-induced reinstatement. During FR1, each nose poke results in a tone and delivery of 0.1 ml 20% sucrose in a well. Responding is then extinguished by eliminating the tone and reward following a nose poke. During cue-induced reinstatement, each nose poke results in a tone, but no sucrose is delivered. At each test stage, rats receive inactivation of PL circuits via clozapine-N-oxide (CNO; 3 mg/kg) or vehicle. Preliminary findings (n=3) show that inactivation of PL-to-VS projections during FR1 expression decreased rewarded well entries, but increased overall non-specific well-entries. Additionally, all rats exhibited longer latency to attempt to collect reward during inactivation of acquisition of cue-induced reinstatement (leaving the nose poke to enter

the well to collect reward). Although preliminary in nature, our results thus far indicate an important role of the PL-to-VS projection in regulation of operant reward seeking, in line with previous work. Further analysis and comparison with diverging targets will reveal selective contributions of subsets of PL networks to execution and suppression of reward seeking, both during and after learning.

Disclosures: **J.P. Caballero:** None. **D.E. Moorman:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Title: Inverse gating of discrimination learning by dopamine D2 receptors in the nucleus accumbens

Authors: *T. SAWADA, Y. IINO, K. YAMAGUCHI, S. YAGISHITA, H. KASAI;
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Abstract: Dopamine 2 receptors (D2R) are densely expressed in the striatum, and are related to the psychotic symptoms of schizophrenia. With its high-affinity binding to dopamine, D2R has implicated in the detection of transient reduction in dopamine concentration (DA dip). However, the nature of D2R-dependent behaviours and cellular mechanisms which can account for the antipsychotic effects of D2R antagonists has been elusive. Here, we found in mice that tone-induced reward-prediction learning in the nucleus accumbens (NAc) was markedly generalized in a D1R-dependent manner, and discrimination learning refined the prediction by DA dip and D2R dependent mechanism. Interestingly, neither DA dip nor D2R was involved in the extinction context. In NAc slice, narrow DA dip (0.4 s), was detected by D2R to disinhibit the adenosine 2A receptor (A2AR) mediated enlargement of dendritic spines of D2R expressing spiny projection neurons (D2-SPNs). CaMKII and A2AR in NAc, which mediated plasticity of D2-SPN, were also required for the discrimination learning, indicating that the DA dip was detected by D2-SPN. Moreover, we found that the discrimination learning was impaired by a repeated methamphetamine treatment, a model of psychosis, and was rescued by D2R

antagonist. Thus, our data demonstrate that D1R and D2R competitively refine the reward prediction, and suggest a novel hypothesis that the inability to learn from the absence of predicted results causes salience misattribution, as seen in subjects with schizophrenia, which can be mitigated by antipsychotics through the D2R-mediated plasticity mechanisms.

Disclosures: **T. Sawada:** None. **Y. Iino:** None. **K. Yamaguchi:** None. **S. Yagishita:** None. **H. Kasai:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Program #/Poster #: 504.13/W2

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant DA035432

Title: Chronic stress causes a lasting increase in relapse-like behavior following punishment-induced abstinence from palatable food seeking, an effect mediated by dopamine D_1-like receptors

Authors: *K. T. BALL, S. HOLBROOK, R. PHELPS, J. ROE;
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Abstract: Long-term success of dietary treatments is low because most individuals relapse to unhealthy eating habits within months of starting treatment. Although chronic stress has long been associated with relapse vulnerability in the clinical literature, relatively few pre-clinical studies have used models of relapse that incorporate a chronic stressor. In previous studies, we added a chronic stress component to two widely used animal models of craving and relapse: the extinction/reinstatement model and the related forced abstinence model. We showed that animals with a history of chronic stress displayed greater relapse to food seeking compared to unstressed rats for up to 1 week following the termination of stress. We also demonstrated that systemic dopamine D_1-like receptor (D_1R) antagonism during chronic stress attenuated the effects of the stress on subsequent relapse-like behavior. Building on these findings, we aimed to determine the effects of chronic stress on relapse to palatable food seeking following punishment-induced (self-imposed) abstinence. Rats were trained to press a lever for highly palatable food reinforcers in daily 2-hr sessions. Delivery of food was accompanied by a 5-s tone + light conditioned stimulus. During a subsequent punishment phase, 50% of the reinforced lever presses resulted in the concurrent delivery of a 0.5-s footshock through the grid floor. Footshock began at 0.12 mA and increased by 0.06 mA every day for a total of 7-8 punishment sessions. To model chronic stress, rats were placed in restrainers (120 min/day) or returned to their home cage (unstressed) after each punishment session. To assess dopaminergic involvement, each group received

injections of either the selective D_1R antagonist SCH-39166 (20.0 μg/kg; i.p.) or vehicle prior to each daily treatment. Cue-induced relapse tests were conducted on the 1st and 8th days after the last session of the punishment phase. Pellet priming-induced relapse tests were conducted on the 8th day following punishment. No significant differences in responding among treatment groups was observed during cue-induced relapse tests on either test day. However, rats with a history of chronic stress displayed increased pellet priming-induced relapse, and SCH-39166 combined with chronic stress prevented this effect. These results are the first to demonstrate that chronic stress causes lasting vulnerability to relapse following punishment-induced abstinence. Moreover, our findings with SCH-39166 are in agreement with our previous studies using other models of relapse and highlight the important role of D_1R signaling in the effects of chronic stress on palatable food-seeking.

Disclosures: **K.T. Ball:** None. **S. Holbrook:** None. **R. Phelps:** None. **J. Roe:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Topic: G.01. Appetitive and Aversive Learning

Support: DGAPA-PAPIIT 201018
Technical assistants Gabriela Vera
Technical assistants Alejandro Rangel-Hernández
Technical assistants Perla Lizeth Chavez Padilla
Technical assistants Shaun Harris

Title: The role of n-methyl-d-aspartate receptors in the insular cortex during a motivational conflict task: Updating from an appetitive to an aversive memory

Authors: *M.-J. OLVERA-CALTZONTZIN, M. I. MIRANDA;
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Abstract: Normally taste is learned in a variety of contexts that could alter its inherent hedonic valence. Thus, sweet taste is inherently appetitive or pleasant and carries positive valence during association; whereas, for example, a mild electric shock is inherently aversive and has negative valence. Furthermore, these two stimuli with opposite valences may also compete during memory updating, from an appetitive to an aversive association. Brain cortical participation during valence processing has been recently proposed during re-learning and memory updating. Particularly, the insular cortex (IC) is involved during taste memory updating as well as during context learning related tasks. Therefore, the purpose of this research was to evaluate the

involvement of NMDA receptors (NMDAR) activity in the IC during a motivational conflict task, based on the inhibitory avoidance (IA) learning procedure, where taste memory was updated from an appetitive/neutral context (chamber no shock) to an aversive one (chamber with electric shock). Accordingly, we used a modified IA chamber that had a graduated bottle at the end of the dark compartment (DC), filled with water or sugar. In this condition rats were pre-exposed to the DC and the next day were subjected to IA acquisition, receiving a mild electric foot shock (negative valence) when entering the DC that also had water or sugar (positive valence). Three parameters were measured during pre-exposure, IA acquisition and IA retrieval: 1) Entry latency to DC, 2) Sugar latency consumption and 3) liquid volume consumption. Rats were bilaterally injected with NMDA (6.8 μM) in the IC, five minutes before IA acquisition. The results indicate that sugar at the end of the DC induced a lower entry latency during IA retrieval; e.g., increasing the latent inhibition of the IA, no changes were observed in groups with NMDA injections. Also, consumption latency decreased when sugar was available at the end of the DC, instead of water; nonetheless, NMDAR activation produced a decrease only for water consumption latency. Furthermore, either water or sugar volume consumption remained similar during retrieval, without any NDMDA effect. Overall, these results indicate that sugar but not water pre-exposure in a context to be aversive (DC), induces an increase in IA latent inhibition, e.g., positive valence, regardless of whether NMDAR are activated. Nevertheless, NMDAR only increased the appetitive response for water under an aversive context, suggesting that sugar increases appetitive memory updating during a motivational conflict task and NMDAR activation increases this memory updating for more neutral stimuli such as water.

Disclosures: M. Olvera-Caltzontzin: None. **M.I. Miranda:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Topic: G.01. Appetitive and Aversive Learning

Support: DA019473
DA038412
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DA041725
DA035589

Title: NMDA receptor-dependent plasticity in the nucleus accumbens underlies acquisition of cued reward-seeking behavior

Authors: M. VEGA VILLAR[1,2], J. C. HORVITZ[1], ***S. M. NICOLA**[2];
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Abstract: Animals learn associations between contextual cues and the natural rewards they predict (e.g., food, water, sex). As a result, reward-predictive cues come to trigger approach to locations where rewards are available. The nucleus accumbens (NAc) is implicated in the expression of such cued reward-seeking behaviors. Consistent with this idea, many neurons in the NAc become excited upon presentation of an already-learned reward-predictive cue (e.g., McGinty et al., *Neuron* 2013). Cue-evoked excitations encode the motivational value of the stimulus and are required for expression of the subsequent approach behavior (e.g., Caref & Nicola, *eLife* 2018; Du Hoffmann and Nicola, *J Neurosci* 2014). However, whether and how cue-evoked excitations emerge during learning has not yet been established. In Experiment 1, we recorded the unit firing activity of NAc core neurons as rats learned to approach a reward receptacle upon presentation of a cue. Our results indicate that cue-evoked excitations begin to increase a few trials before cued approach behavior is detected and they continue to escalate as cued reward-seeking responses become more vigorous.
Because infusion of NMDA receptor antagonists into the NAc during training impairs acquisition of similar cued approach behaviors (e.g., Di Ciano et al., *J Neurosci.* 2001), we hypothesized that the emergence of cue-evoked excitations during cued approach learning is due to NMDA receptor-dependent plasticity within the NAc. In Experiment 2, we performed colocalized simultaneous unit recordings and NMDA antagonist microinfusions in the NAc. We found that the potentiation of learning-related cue-evoked signals in the NAc depends on NMDA receptor-dependent plasticity within this structure, and that this effect is independent of NMDA receptor contributions to behavioral performance. Our results link NAc plasticity, changes in striatal activity and the emergence of conditioned behavior, revealing a neural mechanism via which the NAc participates in associative learning.

Disclosures: M. Vega Villar: None. **J.C. Horvitz:** None. **S.M. Nicola:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant AA026090

Title: Activation of oxytocin receptor expressing neurons in the ventral tegmental area that project to nucleus accumbens can be rewarding or aversive

Authors: *J. PERIS, K. TOTTEN, D. MONTGOMERY, K. A. SCOTT, E. G. KRAUSE; Pharmacodynamics, Univ. of Florida, Gainesville, FL

Abstract: Oxytocin receptors (OXTR) are expressed by nondopaminergic ventral tegmental area (VTA) neurons that project to multiple forebrain targets, including the nucleus accumbens shell (shNAc). We hypothesize that OXTR-expressing VTA glutamate neurons send projections to shNAc that control reward. Male mice (n=4) expressing Cre recombinase under control of the *Oxtr* promoter were unilaterally injected in the NAc with a Cre-inducible retrograde adeno-associated virus (AAV) expressing yellow fluorescent protein (YFP). YFP-labeled soma in the VTA expressed vGluT mRNA, indicating that OXTR-expressing glutamate neurons send projections to the NAc. Next, we bilaterally injected VTA with a Cre-inducible AAV expressing YFP alone (Sham; n=3) or with channel rhodopsin 2 (ChR2; n=4) and bilaterally implanted fiber optics into the shNAc to optogenetically stimulate axons originating from OXTR-expressing neurons in the VTA. Three weeks later, mice were trained to operantly respond for optic fiber stimulation (1 sec of 40 Hz). After 9 sessions, the number of active responses was greater in mice expressing ChR2 relative to Sham (88.5±44.2 vs 10.7±4.8) with lower responding in the inactive port (20.0±7.6 vs 9.3±4.8). The ratio of active responses to total responses was significantly greater in ChR2 vs Sham mice on the last 2 days of testing (0.75±0.03 vs 0.52±0.17; $F(1,5) = 8.29$ $p < 0.05$). However, when a real time place preference paradigm was implemented, the pattern of stimulation greatly affected the amount of time spent on the side paired with optical stimulation. Optical stimulation of 1 sec 40 Hz on/1 sec off significantly decreased time spent on the paired side compared to pretest in ChR2 mice (16.5%±1.66 vs 34.0%±4.96) but not in Sham mice (25.8%±2.98 vs 27.5±3.17; Virus X Test Day $F(1,4) = 10.41$, $p < 0.05$). Conversely, optical stimulation of 1 sec 40 Hz on/9 sec off significantly increased time spent on the paired side compared to the pretest in ChR2 mice (38.0%±3.75 vs 30.1%±1.34) but not in Sham mice (31.6%±2.39 vs 32.0±6.60; Virus X Test Day $F(1,5) = 7.33$, $p < 0.05$). These results suggest OXTR are expressed on glutamatergic VTA neurons whose projection to the shNAc may confer reward or aversion depending on the pattern of neural activity delivered.

Disclosures: J. Peris: None. **K. Totten:** None. **D. Montgomery:** None. **K.A. Scott:** None. **E.G. Krause:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Topic: G.01. Appetitive and Aversive Learning

Support: NSF 1557987
T32 DA037202

Title: Chemogenetic activation of orbitofrontal striatal circuitry increases flexibility in rats that have developed habitual behavior on a modified t maze task

Authors: *J. J. STOTT, K. S. SMITH;
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Abstract: The orbitofrontal cortex (OFC) and medial striatum (MS) are involved in outcome valuation, and these areas are necessary for certain kinds of goal-directed behavior, including sensitivity to reinforcer devaluation. We asked whether chemogenetic activation of this pathway could produce an enhancement of flexible behavior in animals that had already developed a maze-running habit, and if so, what aspects of maze running were affected.
Rats were run on a novel plus maze-type task which consisted of an elevated track with four arms, each with a reward site. To make a correct response and obtain reward, rats had to follow a simple turn-right rule. Reward sites had a unique combination of reward magnitudes (Large or Small), and pellet flavor (Banana or Chocolate).
To characterize the development of habits on this task, three groups of rats were run without surgery, varying in the amount of training they received. Rats received Low, Moderate, or High amounts of training before undergoing three pairings of a pellet reward with LiCl (0.3M) in an empty cage. After devaluation of one of the rewards, rats were returned to the task for 1 session in extinction (Probe), and 5 additional sessions with pellet delivery (ReAcquisition).
An additional group of animals underwent surgery prior to the start of the experiment. These rats were injected with a Cre-containing retrograde virus (CAV-Cre or AAVrg-Cre) into the DMS and a Cre-dependent Gq-coupled DREADD or control virus into the ventrolateral OFC. These rats were given injections of CNO (0.1mg/kg) 30 min prior to the Probe and ReAcquisition sessions.
Rats quickly learned the task, increasing their accuracy over days to >90%. Rats rejected all pellets after 3 LiCl pairings. In the Probe Session, rats were still likely to visit the all the maze arms, indicating habitual behavior. However, the Moderate and Gq rat groups exhibited more pauses before entering the devalued feeder arms, suggesting that there was some recognition of the new outcome value and that OFC-MS activation restored that in highly trained rats.
In Reacquisition, rats in the High training groups continued to turn right on each lap. In contrast, rats in the Low and Moderate training groups slowly developed new a strategy, learning to avoid the devalued arms. The number of non-devalued pellets earned per lap increased over days. This was also true for Gq animals, though to a lesser extent. Therefore, stimulation of DMS-projecting OFC cells was able to partially rescue flexible behavior during trial and error learning after a change in task contingency. Neural recordings in the OFC and DMS are being performed to characterize the neural underpinnings of this change in strategy.

Disclosures: J.J. Stott: None. **K.S. Smith:** None.

Poster

504. Appetitive and Incentive Learning and Memory II

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Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant 4R00DA042102-02

Title: Fos expressing neuronal ensembles in ventromedial prefrontal cortex mediate acquisition of food seeking

Authors: *A. A. GENOVESE[1], R. QUINTANA-FELICIANO[2], G. LOYOLA[3], B. L. WARREN[3];
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Abstract: Aims: We previously found that functionally distinct neuronal ensembles in the ventral medial prefrontal cortex (vmPFC) mediate self-administration and extinction of food seeking in well-trained rats. In the present study, we examined whether neuronal ensembles also mediate acquisition of food seeking.
Methods: We allowed transgenic Fos-LacZ rats to lever press for palatable food pellets. Rats self-segregated into "learners" that pressed more than 50 times in a single session and "non-learners" that failed to press more than 50 times in a single session. We then tested rats' recall of food-seeking in a 15 min probe test intended to reactivate acquisition ensembles and induce Fos and B-Gal expression. We then used vehicle or Daun02 inactivation to selectively ablate Fos-expressing neuronal ensembles within the vmPFC that were associated with acquisition of food seeking. Two days later, we tested the rats' ability to recall the food-seeking memory.
Results: During the induction session, learners pressed the active lever significantly more than non-learners. During the test session, Daun02 inactivation significantly reduced active lever presses in learner rats, but had no effect in non-learners.
Conclusions: Taken together, these data suggest that neuronal ensembles within the vmPFC mediate acquisition of food-seeking.

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Poster

504. Appetitive and Incentive Learning and Memory II

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Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant DA042102
NIDA IRP

Title: Fos-expressing neuronal ensembles projecting from ventromedial prefrontal cortex to nucleus accumbens are activated during acquisition of food seeking

Authors: *G. LOYOLA[1], R. QUINTANA-FELICIANO[1], A. GENOVESE[1], L. F. KANE[2], B. T. HOPE[2], B. L. WARREN[1];
[1]Dept. of Pharmacodynamics, Univ. of Florida, Gainesville, FL; [2]Behavioral Neurosci., Natl. Inst. On Drug Abuse, NIH, Baltimore, MD

Abstract: Aims: We previously found that functionally distinct neuronal ensembles in the ventral medial prefrontal cortex (vmPFC) mediate self-administration and extinction of food seeking in well-trained rats. In the present study, we examined whether neuronal ensembles were activated by acquisition of food seeking. We then tested whether neuronal ensembles associated with acquisition of food self-administration project to different subregions of the nucleus accumbens (NAc).
Methods: We allowed rats to lever press for palatable food pellets. Rats self-segregated into "learners" that pressed more than 50 times in a single session and "non-learners" that failed to press more than 50 times in a single session. We then tested rats' recall of food-seeking in a 15 min probe test intended to reactivate acquisition ensembles and induce Fos. We then characterized these Fos expressing neurons using Fos immunohistochemistry and *in situ* hybridization for *Fos, Vgat,* and *Vglut1*. Lastly, we used the fluorescently labeled retrograde tracer CTb to determine whether acquisition of food-seeking activated vmPFC neuronal ensembles projecting to NAc.
Results: Learners pressed the active lever significantly more in the probe test than non-learners. vmPFC Fos expression was increased in the learners when compared to non-learners. However, the *in* situ analysis revealed that the phenotype of activated neurons did not differ between learners and non-learners. The tracing experiment indicated that activated neurons associated with acquisition of food seeking project to the NAc.
Conclusions: Taken together, these data suggest that neuronal ensembles within the vmPFC are recruited during acquisition of food-seeking. Furthermore, these ensembles are made up of heterogenous populations of neurons, and these neurons project to the NAc.

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Poster

504. Appetitive and Incentive Learning and Memory II

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Program #/Poster #: 504.20/W9

Topic: G.01. Appetitive and Aversive Learning

Title: Transcriptional profiles in reinforcement learning across brain regions reflect associative structure and reward history

Authors: S. BINDAS, C. S. CHEN, D. WEAVER, ***N. M. GRISSOM**;
Univ. of Minnesota, Minneapolis, MN

Abstract: Forming associations between our behaviors and specific positive outcomes they elicit, such as food or social interaction, is critical to survival. However, the intracellular and transcriptional processes that regulate operant learning are very poorly understood, compared to the mechanisms which govern pavlovian associations. To address this, we have examined the induction of transcription in multiple brain regions known to be critical to reinforcement learning in the brains of male and female mice as they underwent operant training. We tested animals who had experienced one of four conditions: a) well trained on a fixed-ratio (FR) operant task, b) had newly acquired the response contingency in the FR task that day, c) received yoked reward with no operant requirement, and d) home cage controls. Using high-throughput qrtPCR arrays, we assessed transcription patterns in the mouse amygdala, nucleus accumbens, and dorsomedial striatum. For this screen we tested forty-six transcripts, including immediate early genes known to be induced in pavlovian learning, transcripts important to dopamine function, and genes which have been linked with autism spectrum disorders, as animal models of autism and humans on the autism spectrum have challenges making reward guided choices. Thus far, we have observed broad transcription patterns that correlated with task learning and reward exposure across experimental groups. In male animals, broad transcriptional signals in the amygdala were lowest in animals who had learned the operant association, compared to yoked animals, suggesting the act of acquiring an operant response may require the suppression of mechanisms that support pavlovian associations. In contrast, transcription in the nucleus accumbens had its strongest relationship to the number of reinforcers an animal received, regardless of the associative contingency (operant or yoked). These results suggest distinct molecular mechanisms operating in the accumbens and amygdala when learning an operant response.

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Poster

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Topic: G.01. Appetitive and Aversive Learning

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Title: Murine genetic variance in muscarinic cholinergic receptor antagonism of fat intake and acquisition and expression of fat-conditioned flavor preferences in three inbred mouse strains

Authors: B. ISKHAKOV, P. DOHNALOVA, J. ISKHAKOVA, T. MUSTAC, A. YUABOV, J. MACANIAN, E. ISRAEL, N. LOCURTO, N. FRANZ, G. FAZILOV, M. SHENOUDA, *R. J. BODNAR;
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Abstract: Muscarinic cholinergic receptor antagonism differentially alters sweet intake as well as the expression (maintenance) and acquisition (learning) of sucrose-conditioned flavor preferences (CFP) in inbred mice. Sucrose and saccharin intakes were significantly and more potently reduced following scopolamine (SCOP) in C57BL/6 and BALB/c mice relative to SWR mice. SCOP significantly reduced the expression of sucrose-CFP in BALB/c, but not C57BL/6 or SWR mice. SCOP eliminated the acquisition of sucrose-CFP in BALB/c mice, reduced its magnitude in SWR mice, but failed to affect this response in C57BL/6 mice. Fat (Intralipid) intake and fat-CFP are robustly elicited in BALB/c, C57BL/6 and SWR mice. Given that the dopamine D1, opiate and NMDA receptor antagonist pharmacological profile of sweet and fat intake and CFP differs across inbred mouse strains, the present study examined whether SCOP differentially altered fat (Intralipid) intake as well as the expression and acquisition of fat-CFP in BALB/c, C57BL/6 and SWR mice. The first experiment evaluated the systemic dose-dependent effects of SCOP (0.1-10 mg/kg) on Intralipid (5%) intake over a 2 h time course in the three strains. Intralipid intake was significantly reduced in all three strains across all doses and the entire time course. In fat-CFP expression experiments, food-restricted mice alternately consumed a flavored (CS+, e.g., cherry Kool Aid, 5 sessions) Intralipid (5%) solution and a differently-flavored (CS-, e.g., grape Kool Aid, 5 sessions) Intralipid (0.5%) solution. Two-bottle CS choice tests with the two flavors mixed in 0.5% Intralipid solutions occurred following vehicle or SCOP at doses of 1 or 5 mg/kg. SCOP minimally altered the magnitude of the expression of fat-CFP in BALB/c and C57BL/6, but not SWR mice. In fat-CFP acquisition experiments, separate groups of BALB/c, C57BL/6 and SWR mice were treated prior to the ten acquisition training sessions with vehicle or 2.5 or 5 mg/kg SCOP doses that was followed by six two-bottle CS choice tests without injections. SCOP eliminated the acquisition of fat-CFP in BALB/c and C57BL/6 mice, and dose-dependently reduced its magnitude in SWR mice. Thus,

muscarinic cholinergic receptor signaling is essential for the learning of fat-CFP in BALB/c and C57BL/6 mice and, to a lesser degree, in SWR mice while maximally inhibiting fat intake in the three strains. Therefore, murine genetic variance differentially modulates muscarinic cholinergic receptor control of sweet and fat intake per se as well as their learned preferences.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 505.01/W11

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant DA034010

Title: Early adolescent adversity inflates periaqueductal gray/dorsal raphe cue responding but diminishes threat signaling in female adult rats

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Abstract: Childhood adversity increases adult risk for stress and anxiety disorders. A contemporary view of the link between early adversity and adult psychiatric disorders is of latent vulnerability. Early adversity reshapes processing in neural circuits underlying fundamental behavioral processes, leaving these circuits impaired and vulnerable through adulthood. We tested the hypothesis that early adolescent adversity (EAA) alters adult threat processing in the ventrolateral periaqueductal gray (vlPAG) and dorsal raphe (DR). Female Long Evans rats received a battery of discrete stressors during early adolescence. In adulthood, control (n = 8) and EAA (n = 12) rats were implanted with drivable microelectrode bundles just above the vlPAG and driven following each session, eventually reaching DR. Single-unit activity was recorded while rats underwent fear discrimination, in which three auditory cues predicted unique foot shock probabilities: danger (p = 1.00), uncertainty (p = 0.375) and safety (p = 0.00). In controls, one population of vlPAG/DR neurons (32/151, ~22%) was excited during cue presentation and a slightly larger population (48/151, ~32%) was inhibited. Cue-excited neurons showed graded cue firing: high to danger, intermediate to uncertainty and low to fear; with regression revealing these neurons signaled threat probability. Cue-inhibited neurons maximally decreased firing to danger and signaled a mix of threat probability and fear output. A larger proportion of units were cue-responsive in EAA rats: cue-excited (49/203, ~24%) and cue-inhibited (84/203, ~41%). Cue-excited neurons from EAA rats showed inflated neural activity to

danger, uncertainty and safety at cue onset and diminished differential cue firing as cues progressed. Yet, these same cue-excited neurons showed reduced threat probability signaling. Cue-inhibited neurons from EAA rats showed exaggerated inhibition to danger in early cue presentation. These same neurons initially signaled a mix of threat probability but switched to exclusively signaling fear output midway through cue presentation. Early adolescent adversity inflates vlPAG/DR activity to threat related cues, reduces flexible signaling of threat probability and favors more rigid signaling of fear output.

Disclosures: M. Moaddab: None. **K.M. Wright:** None. **M.A. McDannald:** None.

Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Program #/Poster #: 505.02/W12

Topic: G.01. Appetitive and Aversive Learning

Support: NIH

Title: Zona incerta gabaergic output controls a signaled locomotor action in the midbrain tegmentum

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Abstract: The zona incerta is a subthalamic nucleus that has been proposed to link sensory stimuli with motor responses to guide behavior, but its functional role is not well established. Using mice of either sex, we studied the effect of manipulating zona incerta gabaergic cells on the expression of a signaled locomotor action, known as signaled active avoidance. We found that modulation of gabaergic zona incerta cells, but not of cells in the adjacent thalamic reticular nucleus, fully controls the expression of signaled active avoidance responses. Inhibition of zona incerta gabaergic cells drives active avoidance responses, while excitation of these cells blocks signaled active avoidance by inhibiting cells in the midbrain pedunculopontine tegmentum (PPT), not by inhibiting cells in the superior colliculus or posterior thalamus. The effects of manipulating zona incerta gabaergic cells on signaled active avoidance are similar to the effects of manipulating substantia nigra pars reticulata gabaergic cells -a main output of the basal ganglia. Thus, gabaergic outputs from the zona incerta and the basal ganglia provide independent channels to regulate a signaled locomotor action in the PPT, which may operate depending on behavioral contingencies.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Title: Dorsolateral periaqueductal gray activates antipredatory neural responses in the amygdala in foraging rats

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Abstract: The dorsolateral division of the periaqueductal gray (dlPAG) and the amygdala are known to direct defensive responses (Bandler & Shipley, 1994; Fanselow, 1994). We have previously reported that electrical stimulation of the dlPAG caused rats foraging for food in an ecologically-relevant environment to escape to the safe nest (Kim et al., 2013). This fleeing response was blocked by amygdalar lesions and inactivation, suggesting that the dlPAG-amygdala pathway is crucial to the brain's innate defensive system. Recently, we also found that dlPAG neurons responded to a looming robotic predator and that optogenetic excitation of the dlPAG neurons elicited neural activity in the amygdala. However, the specific function of the dlPAG-amygdala neurotransmission when animals encounter predatory risks is unknown. To address this issue, we employed single unit recording and optogenetic techniques in our 'approach food-avoid predator' paradigm (Choi & Kim, 2010; Kim et al., 2018). Specifically, male Long-Evans rats were implanted with tetrode arrays into the BLA (basolateral amygdala) or CeA (central amygdala) and injected with AAV-CaMKIIα-hChR2-EYFP into the dlPAG. After recovery, rats maintained on ~85% normal body weight underwent successive stages of habituation, baseline foraging, and optogenetic dlPAG stimulation (473 nm; 10 ms pulses at 20 Hz; 2 s) and robot (Lego Mindstorms) testing, during which BLA and CeA units were collected. We found that optical dlPAG stimulation increased neuronal activity in both BLA and CeA and caused naive rats approaching a food pellet to instantly flee to the nest. The dlPAG photostimulation-responsive BLA neurons also exhibited rapid phasic spiking to the looming robot whereas the photostimulation-responsive CeA neurons showed delayed tonic spiking.

Furthermore, higher proportions of photostimulation-responsive neurons in BLA and CeA also reacted to the robot compared to photostimulaton-nonresponsive neurons. These results suggest that functional interaction between dlPAG and amygdalar neurons subserve antipredatory defensive mechanisms.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Topic: G.01. Appetitive and Aversive Learning

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Title: Role of the cerebellum-periaqueductal grey pathway in fear conditioning

Authors: ***E. PACI**[1], C. LAWRENSON[1], R. MORAN[2], B. LUMB[1], R. APPS[1];
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Abstract: Auditory cue fear conditioning is a well-established behavioural paradigm to study the neural networks involved in acquisition, expression and extinction of fear. Indeed, the role of areas such as prefrontal cortex, amygdala and periaqueductal grey (PAG) has now been characterised in the context of conditioned fear. More recently the cerebellum has also been included in this 'fear network', as studies have shown that it is implicated in the acquisition of fear memories as well as in the expression of fear-conditioned freezing behaviour.Anatomical and physiological studies from our laboratory and other groups have shown that the PAG, specifically the ventrolateral (vl) sector, projects to vermal lobule VIII of the cerebellar cortex, and that the medial cerebellar nuclei in turn projects to the vlPAG. However, the role of this reciprocal pathway in fear conditioning is unclear.To better understand the functional role of these connections we have recorded local field potential (LFP) activity simultaneously from the cerebellum and PAG while rats were exposed to an auditory cue conditioned fear paradigm.Preliminary results show in the cerebellum that, relative to baseline, there is an increase in LFP power in delta and theta frequencies during acquisition, and a decreased power in these frequencies during extinction. In the PAG there is also an increase in delta power during acquisition that is reversed during extinction, but no change in theta power relative to baseline. The present results suggest both similarities and differences in the pattern of LFP activity in the cerebellum and PAG during fear conditioning.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Topic: G.01. Appetitive and Aversive Learning

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Title: Anatomical and functional characterization of RMTg-projecting PFC neurons

Authors: E. M. STARR[1], W. N. WAYMAN[2], J. J. WOODWARD[2], L. CHANDLER[3], ***E. J. GLOVER**[1];
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Abstract: Exposure to aversive stimuli is associated with enhanced activity within the rostromedial tegmental nucleus (RMTg) and activation of the RMTg facilitates aversive responding. The medial prefrontal cortex (mPFC) provides input to the RMTg and activity within this region has also been implicated in many of the same endpoints. However, little is known about the anatomy and function of this projection. To better characterize the density of the mPFC input to the RMTg, Long-Evans rats were injected with a retrograde tracer into the RMTg. Two weeks after injection, cell body labeling was apparent throughout the entire medial and orbital walls of the PFC and spanned the entire rostrocaudal extent of the region. Labeling was also observed in the anterior insular cortex. RMTg-projecting cell bodies were restricted primarily to cortical layer V, though a small number of cells were also consistently observed in the deepest portion of layer VI. Quantification of tracer labeled neurons relative to NeuN labeling found that approximately 14.21% ± 0.38 of layer V prelimbic mPFC neurons projected to the RMTg. Quantification of other subregions is ongoing. RNAscope combined with retrograde tracing revealed a subpopulation of RMTg-projecting mPFC neurons expressing either D1, D2, or both D1 and D2 dopamine receptors. Stimulation of RMTg-projecting mPFC inputs using in vivo optogenetics produced significant real-time place avoidance, the magnitude of which was similar to that produced by stimulation of lateral habenula inputs to the RMTg ($p \leq 0.01$) indicating that activation of this pathway can induce aversive responding. In addition, rats

presented with a shock or a tone predictive of shock exhibited a significant increase in cFos expression in RMTg-projecting mPFC neurons compared to rats exposed to neutral stimuli ($p \leq 0.05$). Using whole-cell patch-clamp slice electrophysiology, we found that exposure to a single episode of 10 consecutive footshocks resulted in a significant decrease in the frequency of evoked firing in RMTg-projecting prelimbic neurons compared to unshocked controls ($p \leq 0.0001$). Ongoing work is exploring the effect of repeated footshock on structural plasticity in mPFC-RMTg neurons. Together, these results demonstrate involvement of mPFC input to the RMTg in the behavioral response to aversive stimuli, and further reveal significant plasticity as a result of exposure to aversive stimuli. Alterations within this neural circuit may be critically involved in neuropsychiatric illnesses associated with disruption of the balance between signaling of rewarding and aversive outcomes including addiction and mood disorders.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Title: Striatal beta oscillation and neuronal activity in the primate caudate nucleus differentially represent valence and arousal under approach-avoidance conflict

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Abstract: An approach-avoidance (Ap-Av) conflict arises when an individual has to decide between acceptance and rejection of a compound offer that has positive and negative attributes. During the conflicting judgment of likes and dislikes, motivational responses simultaneously emerge and influence reaction times and the frequency of behavioral errors. Based on the differential influences of reward and aversiveness, we dissociated the neural processes of valence and arousal responding to the conflict offers. The primate caudate nucleus (CN) has been

implicated in affective judgment, but it is still unclear how the CN neural responses represent the decision-related variables. To address this issue, we recorded spikes and local field potentials (LFPs) from the CN while the subject macaques perform the Ap-Av conflict task. In this task, monkeys reported their decisions by moving a joystick within 3 seconds to the Ap or Av target. We analyzed 450 unit and 667 LFP activities recorded during the performance of the Ap-Av conflict task, and 120 units and 230 LFPs recorded during the approach-approach (Ap-Ap) conflict task. With the trial-by-trial spike and beta oscillatory LFP activities, we performed all-possible subset regression analyses using five selected behavioral variables, consisting of the offered reward size (Rew), offered airpuff size (Ave), value judgment (ChV: chosen value), reaction time (RT) and behavioral performance (FOE: frequency of omission error). By comparing the unit and beta responses, we found differences in the groups representing value judgment and arousal responses. Whereas CN units represented both positive and negative values (positive: n = 26, negative: n = 14), the beta responses almost exclusively represented positive value (positive: n = 93, negative: n = 1), exhibiting a significant difference in the proportion (Fisher's exact test, $P < 0.001$). CN units also represented both positive and negative FOE (positive: n = 17, negative: n = 9), but the beta responses representing FOE were almost exclusively positive (positive: n = 22, negative: n = 1), leading to a significant difference in the proportion (Fisher's exact test, $P < 0.05$). We further confirmed that those representations were preserved in the Ap-Ap task in which the subjects made decisions only by reward sizes. These dissociable features of unit and beta responses suggest distinctive roles of CN beta oscillations in facilitating positive value judgment and suppressing arousal motivation, whereas specific CN neurons respond to a broader range of features in decision-making under conflict.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Topic: G.01. Appetitive and Aversive Learning

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Title: Medial prefrontal cortex projection to lateral habenula is functional and modulated by dopamine

Authors: *H. LI[1], J. TSAI[1], A. BUXBAUM[1], Y. AYOUB[1], R. MALINOW[2];
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Abstract: Lateral habenula (LHb) neurons are activated by aversive stimuli that may normally participate in negative reinforcement learning. As LHb hyperactivity may contribute to depression, identifying and characterizing excitatory inputs to the LHb is important. The medial prefrontal cortex (mPFC) participates in various higher cognitive functions that could modulate aversive coding. While previous work showed that mPFC neurons send projections to LHb, their function has not been well studied. Here we report that mPFC neurons make long range excitatory synaptic projections to LHb modulated by dopamine (DA). Anterograde labeling by injecting AAV-synaptophysin-citrine in the mPFC show synapses in LHb. To test for functional connections, we injected AAV-ChR2-tdTomato in mPFC and AAV-GCaMP6f in LHb. Three weeks later, we prepared LHb slices and imaged with two-photon microscopy. Blue light pulses evoked responses in LHb cell bodies and dendrites, largely blocked by NBQX. Such responses were also reduced by dopamine. By injecting retro-AAV-ochief-tdTomato in LHb, using whole-cell recordings and two-photon microscopy imaging in mPFC slices, we find that LHb projecting neurons reside mostly in layer 5 of mPFC and make strong excitatory and inhibitory local connections. Overall, we have identified a population of mPFC neurons that make local circuit connections within mPFC and functional LHb connections negatively modulated by dopamine. Such mPFC inputs may control an LHb-VTA mutual inibition circuit.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Title: Connections of the laterodorsal tegmental nucleus with the medial prefrontal cortex and habenular-interpeduncular-raphe system

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Abstract: The laterodorsal tegmental nucleus (LDTg) is an underexplored major cholinergic cell group in the periventricular mesopontine tegmentum, traditionally thought to be involved in

mechanisms of arousal, induction of REM sleep, and the control of the firing pattern of midbrain dopamine cells. Nowadays, there is increasing evidence that LDTg is also engaged in mechanisms of anxiety/fear and promotion of emotional arousal under adverse conditions. Interestingly, LDTg appears to be connected with other regulators of aversive motivational states, including the medial prefrontal cortex (mPFC), lateral habenula (LHb), medial habenula (MHb), interpeduncular nucleus (IP), and median raphe nucleus (MnR). However, the circuitry between these structures has hitherto not been systematically investigated. Here, we placed iontophoretic injections of retrograde or anterograde tracers into the LDTg, LHb, IP, MnR and mPFC of male Wistar rats. We also examined the transmitter phenotype of LDTg afferents to IP by combining retrograde tracing with immunofluorescence and in situ hybridization techniques. We found that LDTg receives abundant inputs from all major subregions of the mPFC. Robust direct LHb inputs to LDTg mainly emerged from the medial division of the LHb (LHbM), which also receives minor axonal inputs from LDTg. MHb is indirectly linked to the LDTg via the MHb-IP axis. The reciprocal connections between IP and LDTg displayed a pronounced lateralized organization, with LDTg inputs to IP being predominantly GABAergic or cholinergic and mainly directed to the contralateral IP. Moreover, we disclosed reciprocal LDTg connections with structures involved in the modulation of hippocampal theta rhythm including the oral part of the pontine reticular nucleus, MnR, nucleus incertus, and supramammillary nucleus. Our findings indicate that the habenula is linked with the LDTg either by direct bilateral projections from/to LHbM or indirectly via the MHB-IP axis. These findings support a potential role of LDTg in the processing of aversive information. Moreover, they further characterize LDTg as part of an authentic state-setting neuromodulatory projection system, and LHb and PFC as master-controllers of such systems, exposing that both are settled to impact not only dopaminergic and serotonergic, but also cholinergic modulatory systems.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Topic: G.01. Appetitive and Aversive Learning

Title: Quantitative determination of the GABAergic cell number in the lateral and basal nuclei of the amygdala using unbiased stereology in mice

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Budapest, Hungary, Budapest, Hungary; [2]Inst. Exp Med. Hungarian Acad Sci., Budapest, Hungary

Abstract: The lateral and basal nuclei of the amygdala belong to the cerebral cortex, a brain structure in which the majority of neurons are glutamatergic excitatory neurons giving rise to both local collaterals and long-range projections. In addition to these neurons, distinct types of GABAergic inhibitory cells are also present in all cortical networks. Evidence suggests that the network operations in the lateral and basal nuclei during both physiological and pathological processes are under tight control of GABAergic inhibition. Yet, there is no data available how many GABAergic cells are present in these two nuclei and what is the ratio of distinct GABAergic cell types. To quantify the number of GABAergic neurons within the lateral and basal amygdala nuclei, we applied unbiased stereology with the aid of optical fractionator on tissue samples taken from Vesicular GABA Transporter (VGAT)-IRES-Cre mice crossed with a reporter mouse line, Gt(ROSA)26Sor_CAG/LSL_ZsGreen1. The borders of the lateral and basal nuclei was determined by revealing cholinergic afferents. We found that in the lateral nucleus the ratio of VGAT+ neurons were between 16-17% and 14-18 % in male and female mice, respectively. In the basal nucleus, a significantly higher ratio of GABAergic cells has been found: 23-24% in males and 21-23% in females. In addition, using immunocytochemistry on sections prepared from distinct transgenic mouse lines (PV-Cre, SOM-Cre, VIP-Cre, NPY-Cre), where interneurons were visualized upon injection of DIO-EYFP construct packed into AAV, we estimated the ratio of different interneuron types within the GABAergic cell populations. Our data show that there is no major difference in the number of GABAergic neurons between the two hemispheres or the two sexes in mice. Defining the exact number of GABAergic cells as well as the ratio of distinct inhibitory cell types in the lateral and basal amygdala nuclei may pave the way for further studies investigating the changes in inhibitory cell populations that may occur in different mental disorders such as anxiety, PTSD or schizophrenia.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Title: Whole-brain mapping of neuronal activation during formation, consolidation and retrieval of aversive memories

Authors: *A. FRANCESCHINI[1], A. COSTA[2], I. COSTANTINI[1], B. RANI[2], G. MAZZAMUTO[1], A. P. DI GIOVANNA[1], P. BLANDINA[2], M. B. PASSANI[3], F. S. PAVONE[1], L. SILVESTRI[1];
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Abstract: The understanding of neuronal and molecular behavioural mechanisms that concern fear and stress have received wide coverage in the last years and various preclinical studies have addressed the treatment for patients affected by mental disorders. The central histaminergic system is an important modulator of memory related to adverse events and the use of antihistaminic drugs in the treatment of the abovementioned diseases is being currently studied often as a prelude to the investigation of effects on anxiety.
In this context, it is essential to understand the spatio-temporal frames allowing the central nervous system to organize behavioural responses associated with adverse events. For this purpose, we analyze whole-brain neuronal activation patterns involved in aversive memory at single-cell resolution.
Fear learning models have been very useful for studying memory consolidation as a whole. Here, we use a classical paradigm for passive inhibitory avoidance (step-through), where mice learn to avoid an electrified cage compartment, analysing whole-brain neuronal activation patterns in both male and female subjects at selected time points (immediately after foot shock, after 1 day, after 1 week). To this end, we use a transgenic mouse model (Fos-TRAP), where permanent expression of a fluorescent protein (tdTomato) is induced in transiently activated neurons (expressing the immediate early gene c-fos) by injection of tamoxifen. To quantify the presence of c-fos-positive cells in an unbiased and comprehensive way, we use the light-sheet microscopy coupled with chemical tissue clearing. This approach does not require sample cutting and enables three-dimensional extensive mapping of activated neurons across the entire mouse brain. Finally, we selectively label histamine-positive neurons in the previously clarified Fos-TRAP brains with whole-mount immunohistochemistry. In this way we quantify the number of histaminergic neurons recruited during different memory phases and localize them with high-throughput algorithms. The combination of behavioral, transgenic, optical and computational methods presented here allows to examine different activation patterns at the selected time points, representing an important tool to understand the neuronal pathways involved in formation, consolidation and retrieval of emotional memories.

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Poster

505. Fear and Aversive Learning and Memory: Circuits II

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Title: Lsfmpy: Open-source toolkit for brain-wide neural activity mapping in optically cleared mouse brain

Authors: *S. BEDNAREK[1], N. JERMAKOW[1], M. STEFANIUK[1], M. PAWŁOWSKA[1], R. REHMAN[2], K. NOWICKA[1], L. BIJOCH[1], F. ROSELLI[2], D. K. WÓJCIK[1], P. MAJKA[1]; [1]Nencki Inst. of Exptl. Biol., Warsaw, Poland; [2]Dept. of Neurol., Ulm Univ., Ulm, Germany

Abstract: The emergence of effective tissue clearing methods enabled volumetric imaging of intact biological samples on unprecedented scale. For neuroscience, the key advantage is the ability to analyze interdependent activity of large populations of neurons in whole-brain context. However, a strong limiting factor of this approach is the lack of adequate computational tools for systematic handling and analysis of the terabytes of data generated in the process. We propose an open-source solution that combines a data model for efficient storage and retrieval of imaging data with multimodal registration pipeline and deep-learning based methodology for object detection and quantification. The data container builds on the Hierarchical Data Format 5 (HDF5) and transforms a series of 2D images, obtained from light sheet fluorescence microscopy (LSFM), into one three dimensional object with precisely defined spatial attributes (voxel spacing, physical coordinates and anatomical orientation). Internally data are structured as a precomputed pyramid of resolutions, facilitating all further processing by providing spatially-aware access to the image across multiple scales. To overcome challenges of multimodal registration, for which typically used metrics, such as mutual information, do not yield satisfactory results, we utilized anatomical label maps to guide the registration process. To this end, Deep Convolutional Neural Networks (DCNN) were trained on manually curated datasets to segment out main white matter tracts, dentate gyrus and the brain outline. We observed significant improvement of the registration accuracy, especially for smaller structures. We also deployed a 3D UNet DCNN to detect c-Fos positive nuclei in iDISCO cleared mouse brains. The pipeline was applied to over 40 sets of images of whole mouse hemispheres from two independent behavioral experiments, where patterns of c-Fos expression were investigated to elucidate neural activity in alcohol addiction and in appetitive and aversive learning paradigms. In addition, we processed LSFM images of virally injected mice, where we evaluated ZSGreen positive cells in cortex and hypothalamus. The results demonstrate that the developed

computational pipeline is suitable for analyzing voluminous datasets collected with modern imaging techniques.

Disclosures: **S. Bednarek:** None. **N. Jermakow:** None. **M. Stefaniuk:** None. **M. Pawłowska:** None. **R. Rehman:** None. **K. Nowicka:** None. **L. Bijoch:** None. **F. Roselli:** None. **D.K. Wójcik:** None. **P. Majka:** None.

Poster

505. Fear and Aversive Learning and Memory: Circuits II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 505.12/W22

Topic: G.01. Appetitive and Aversive Learning

Support: JST ERATO (JPMJER1801)
JSPS Grants-in-Aid for Scientific Research (18H05525)
The Human Frontier Science Program (RGP0019/2016)

Title: *In vivo* whole cell recordings from the amygdala

Authors: ***Y. SATO**, Y. IKEGAYA;
The Univ. of Tokyo, Tokyo, Japan

Abstract: The basolateral amygdala (BLA) is a brain deep region that contributes to emotional processing and may be activated together with the hippocampus. For example, the BLA and the dorsal hippocampus are coactivated during emotional memory consolidation. However, the neural basis of such coactivation has not been addressed, mainly because it is difficult to identified projecting neurons using extracellular recordings, which are widely used to record neuronal firing activity. On the other hand, the *in vivo* patch-clamp technique, an intracellular recordings, enables us to record synaptic inputs and label the projection of the recorded neurons. However, there are few reports using *in vivo* whole-cell recordings from the BLA because it is difficult to attain giga-ohm seal, which is a critical step for the whole-cell mode, because of impurities on pipette tips. Here, we have developed a new method to achieve whole-cell recording from *in vivo* mice deep brain regions. We elaborated double tubes; one is a guide cannula for patch-clamp pipettes, and the other is a tissue-boring stick. Using them, we more easily achieved *in vivo* whole-cell recordings from deep brain regions because the pass length for which the pipettes needed to go through the brain parenchyma were reduced. In this poster, we will present examples of recordings from BLA neurons which is located about 4 mm deep from the brain surface, together with recordings of local field potentials from the dorsal hippocampus.

Disclosures: **Y. Sato:** None. **Y. Ikegaya:** None.

Poster

505. Fear and Aversive Learning and Memory: Circuits II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 505.13/W23

Topic: G.01. Appetitive and Aversive Learning

Support: NIH Grant 1R15MH107008

Title: Extended amygdala circuits are differentially activated by context fear conditioning in male and female rats

Authors: L. URIEN, R. NORDLICHT, ***E. P. BAUER**;
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Abstract: The bed nucleus of the stria terminalis (BNST) contributes to anxiety-like behaviors, responses to stress, and the expression of context fear conditioning. However, most of these behavioral studies have been performed in male rodents, whereas it is known that the BNST is a sexually dimorphic structure. We thus evaluated the contribution of the BNST to context fear expression in female rats. Animals (male and female adult Sprague Dawley rats) received three unsignaled shocks (1 sec, 0.5mA), or no shocks as a control. 24 hours later, they were tested for the expression of context fear for 10 minutes. 45-60 minutes later, they were perfused and brains processed for immunohistochemistry to label ARC- or FOS-positive cells as markers of neuronal activity. Fear conditioned male and female rats exhibited similar levels of freezing behavior during testing. Context fear expression was associated with greater numbers of FOS-positive and ARC-positive cells in the anterolateral portion of the BNST (BNST_AL) compared with no-shock controls or homecage controls in male rats. However, no difference was observed in FOS or ARC immunoreactivity between groups in females. Rather, we observed increased neuronal activity, quantified by FOS expression, in the central nucleus of the amygdala (CE) in female rats. However, bilateral non-specific extensive lesions of the BNST with ibotenic acid (6mg/μL concentration, 0.3μL per side) blocked expression of context fear expression in both sexes, suggesting that another portion of the BNST, and a different extended amygdala circuit, could be necessary for the expression of context fear in female rats. To test this hypothesis, we are using optogenetic strategies to investigate the contribution of the BNST_AL - CE pathway in both males and females to cued and context fear conditioning. These data contribute to our understanding of the neural circuits underlying context fear learning and expression in females.

Disclosures: **E.P. Bauer:** None. **L. Urien:** None. **R. Nordlicht:** None.

Poster

505. Fear and Aversive Learning and Memory: Circuits II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 505.14/W24

Topic: G.01. Appetitive and Aversive Learning

Support: NIH grant 1R15NH107008
Beckman Scholars Program

Title: Anatomical and functional characterization of ventral subiculum projections to the BNST

Authors: *L. URIEN, S. COHEN, R. NORDLICHT, E. P. BAUER;
Neurosci., Barnard Col. of Columbia Univ., New York, NY

Abstract: The ventral subiculum (vSUB), a major output of the hippocampus, contributes to the acquisition and expression of fear conditioning and regulates responses to stress through inhibition of the HPA axis. The bed nucleus of the stria terminalis (BNST) is necessary for the expression of context fear conditioning and anxiety-like behaviors. It has also been implicated in processing stressful events and unpredictable threats. Interestingly, despite the anatomical connectivity of these two brain structures and their common involvement in fear conditioning, the projection from the vSUB to the BNST has not been well-characterized. Here, using a combination of retrograde tracing techniques, behavioral testing and quantification of neuronal activity with FOS immunohistochemistry, we characterized the output from the vSUB to the BNST. Animals (adult male Sprague Dawley rats) received infusions of cholera toxin subunit B fused to the fluorescent marker Alexa-488 into the BNST. We first show that outputs from the vSUB to the BNST are organized topographically, with more anterior portions of the vSUB projecting to more anterior portions of the BNST such as the anteromedial BNST, while the posterior vSUB projects to the posterior BNST including the medial and ventral portions. Next, we assessed the contribution of this pathway to context fear conditioning. Two weeks after surgery, animals underwent context fear conditioning using a standard protocol of 3 unsignaled footshocks (1 sec, 0.5mA), or no footshocks as a control. 24 hours later, they were placed in the conditioning chamber and freezing behavior was assessed for 10 min. 45-60 min later, they were perfused and brains processed for FOS immunohistochemistry. Animals receiving footshocks on training day froze significantly to the context on testing day. Both the overall number of FOS-expressing neurons in the vSUB, as well as the percentage of BNST-projecting vSUB neurons expressing FOS were significantly higher in fear-conditioned animals compared with controls. These data contribute to our understanding of how context fear information is relayed from the ventral hippocampus to the BNST.

Disclosures: L. Urien: None. **E.P. Bauer:** None. **S. Cohen:** None. **R. Nordlicht:** None.

Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.01/W25

Topic: G.02. Motivation

Support: NIH Grant RO3DA045281

Title: Amphetamine sensitization under reward uncertainty has opposing effects on conditioned approach and conditioned reinforcement to serial cues

Authors: *K. A. CAPLAN, A. S. KNES, C. CLIBANOFF, H. O. RODRÍGUEZ-CRUZ, C. M. FREELAND, M. J. F. ROBINSON;
Wesleyan Univ., Middletown, CT

Abstract: Pathological gambling is a behavioral disorder affecting 1-2% of the U.S. adult population. Gambling games such as slot machines persistently expose players to audiovisual stimuli (e.g., celebratory sounds, flashing lights, spinning wheels) prior to and during reward delivery. Over time, these cues may become attractive, motivating individuals to continue playing. In those affected by gambling addiction, these reward-paired cues may also trigger cravings and relapse. However, such cues unreliably predict reward outcomes by appearing both in the presence and absence of a reward. Although their predictive value is degraded under uncertainty, animal studies suggest that the attractiveness of these cues is heightened as evidenced by heightened sign-tracking behavior in rats. Repeated exposure to drugs of abuse such as amphetamine can further sensitize the underlying mesolimbic dopaminergic circuits, resulting in even greater incentive value attributed to these cues. Here, we explored the impact of reward uncertainty (probability and magnitude) and prior amphetamine sensitization on incentive salience attribution to serial Pavlovian cues that vary in degree of predictive and incentive value. Male Sprague-Dawley rats were exposed to repeated injections of either amphetamine (1 to 4 mg/kg) or saline over a period of 14 days. After two weeks of incubation, rats were trained in a Pavlovian autoshaping task involving two sequential lever + distinct auditory cues (CS1, CS2) under either Certain (100% -1) or Uncertain (50%-1-2-3) reward conditions. During autoshaping, sign-tracking to the CS1/CS2 levers versus goal-tracking to the pellet-dispensing magazine was assessed. The relative reinforcing properties of either CS1 or CS2 was evaluated next with a one-day conditioned reinforcement task. Rats then underwent autoshaping again to assess the impact of acute amphetamine or nicotine exposure on cue attraction. Our results suggest that Uncertainty enhanced attraction toward the more reward-proximal cue (CS2). However, prior sensitization and Uncertainty reversed this effect, enhancing attraction toward the more predictive reward-distal CS1. Both the CS1 and CS2 acquired conditioned reinforcing properties, despite the CS2 being otherwise ignored in all groups besides the Uncertain reward condition.

However, sensitization and Uncertainty resulted in significantly more interaction with the CS2 lever upon its presentation. This observed discrepancy in cue attraction and rewarding value suggests a possible dissociation between the attractiveness of a cue and its rewarding qualities, particularly for cues proximal to reward delivery.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.02/W26

Topic: G.02. Motivation

Support: NIH ID R03DA045281

Title: Optogenetic inhibition of the AIC and OFC during risky decision making

Authors: *A. S. KNES[1], C. M. FREELAND[2], K. A. CAPLAN[1], M. J. F. ROBINSON[1]; [1]Psychology, [2]Biol. Dept., Wesleyan Univ., Middletown, CT

Abstract: Adaptive decision-making is a complex process that often requires weighing the costs and benefits associated with different options of varying reward magnitudes and probability. The ability to integrate information regarding the probability of reward, loss, and/or adverse consequences requires the cooperation of multiple neural operations to guide optimal behavior. The anterior insular cortex (AIC) and orbitofrontal cortex (OFC) have been implicated in outcome evaluation and decision-making. However, the temporal and functional involvement of these regions in processing and tracking outcomes under risky and uncertain conditions remains largely unknown. In the present study, female rats were trained on a risky decision-making task involving the choice between a Safe option that offered a small, certain reward (1 sucrose pellet) and a Risky option that offered a large, certain reward (3 pellets) with an uncertain and increasing risk of punishment across each session (0%, 25%, 75% risk of foot shock). Animals were trained on this task daily until establishing stable baseline performance. To examine the roles of the AIC and OFC throughout the decision-making process, the AIC or OFC was optogenetically inhibited, via activation of halorhodopsin using green laser light (532 nm), at one of five discrete time points throughout the task: pre-choice, post-choice following Risky punished outcomes, post-choice following Risky unpunished outcomes, post-choice following Safe choices, and between choice trials. The impact of AIC or OFC inhibition at each of the five time points on the proportion of risky choices was compared both within and between animals. Our results suggest that OFC inactivation during post-choice risky unpunished outcomes increased risky behavior despite the increasing likelihood of foot shock. We found no effect of

laser inhibition during inter-trial intervals, verifying that laser inhibition did not produce non-specific or carry-over effects on choice performance during the task. While it is generally accepted that the prefrontal cortex is implicated in decision-making, the manner by which specific cortical regions influence risky behavior and the temporal window in which they act remains largely unknown. These results help address that gap with the potential of providing a better understanding of the pathologic mechanisms involved in maladaptive decision-making.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.03/W27

Topic: G.02. Motivation

Support: NIDA Grant R03DA045281

Title: Reward uncertainty elicits cue-triggered craving for predictive and incentive cues

Authors: *N. ROME, J. M. CHABOT, T. PENG, H. XU, M. MUSTO, M. J. F. ROBINSON; Wesleyan Univ., Middletown, CT

Abstract: Flashing lights and sounds in gambling settings are repeatedly associated with reward outcomes. Even though these cues are often presented in the absence of reward, they become attractive and acquire the ability to increase the desire to gamble. It is believed that the reward uncertainty of gambling attributes excessive motivational value to these cues, thereby contributing to the urge to gamble. Cues preceding rewards contain both predictive and incentive value. Previous research suggests that while reward uncertainty degrades a cue's predictive value, it simultaneously increases its incentive value. Here we use a Pavlovian-to-Instrumental Transfer design in rats to study how reward uncertainty affects the ability of these cues' values to induce craving. Trials in the Pavlovian training sessions consisted of the presentation of an auditory cue (CS1) for 8 seconds, followed by another distinct auditory cue (CS2) concomitant with the last 4 seconds of the CS1 ending with a reward outcome that was either certain or uncertain in probability and magnitude. In marking the beginning of each trial, the CS1 takes on the majority of predictive value. The CS2 adds little predictive information but its temporal proximity to the reward-event lends it mostly incentive value. During subsequent instrumental training, rats were trained to press an active lever over a control lever to receive a sugar pellet. Finally, animals were given access to levers under extinction and the CS1, CS2, and CS1+CS2 were presented in a random counterbalanced order. Cue-triggered craving was measured by spikes in active lever presses and magazine entries during cue presentations. Our results indicate

that rats in the uncertain reward condition exhibited surges of reward-seeking behavior during CS1, CS2, and CS1+CS2 presentations. In contrast, animals in the certain condition only displayed signs of increased craving during the CS1 and CS1+CS2 presentations, and were unaffected by isolated CS2 presentations. These findings suggest that even though reward uncertainty degrades predictive value, it imbues cues with greater incentive value, rendering them capable of inducing cue-triggered craving. These results help us understand how cues can induce a strong urge to continue gambling.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.04/W28

Topic: G.02. Motivation

Support: NSERC Grant RGPIN-2016-06703

Title: Frequency response of optically stimulated, midbrain dopamine neurons

Authors: ***P. SHIZGAL**[1], V. PALLIKARAS[1], F. CARTER[1], D. N. VELÁZQUEZ-MARTINEZ[2], A. ARVANITOGIANNIS[1];
[1]Psychology / CSBN, Concordia Univ., Montreal, QC, Canada; [2]Dept. de Psicofisiologia, Univ. Nacional Autonoma de Mexico, Mexico City, Mexico

Abstract: Rodents will work indefatigably to trigger optical stimulation of midbrain dopamine (DA) neurons. It has not yet been established definitively how the parameters of the optical pulse train translate into the DA firing rate and the intensity of the rewarding effect. These functions must be determined in order to model and optimally manipulate the optical intracranial self-stimulation (ICSS) phenomenon. We characterized frequency-following properties of optically stimulated DA neurons by psychophysical means. Viral transfection and Cre-lox recombination were used to drive expression of Channelrhodopsin-2 in midbrain DA neurons of male TH-Cre rats. A chronically implanted optical fiber was aimed at the ventral tegmental area. The rats were trained to accumulate time on a response clock so as to obtain the optical reward: Depressing a lever for a cumulative time of 2 s triggered delivery of a 1 s train of 31.6 mW, 462 nm optical pulses. The dependent measure was time allocation (TA): the proportion of trial time that the lever was depressed. The pulse duration was fixed within the 50-s trials and stepped downwards in eight equal proportional steps from trial 2 to trial 10 of each sweep; trial 1 was a warm-up trial offering the same pulse duration as trial 2. Ten sweeps were run in each test session, and at least five sessions were run at each pulse frequency. The position of the TA-vs-pulse-duration (TA-d)

curves along the pulse-duration axis served as the scale for estimating the firing-rate changes produced by variation of the pulse frequency. This scaling method is analogous to the one developed by Solomon et al. (Behav. Brain Res., 292, 327-341) for electrical ICSS. Decreasing the optical pulse duration reduces the time available for the photocurrent to reach the firing threshold, thus shrinking the size of the region in which DA neurons are fired and the number of activated neurons. Thus, reductions in pulse duration compensate for, and can serve to scale, increases in firing rate. In 3/5 cases, increasing the pulse frequency from 7-40 pulses per second (pps) shifted the TA-d curves leftwards, implying that the DA neurons fired more frequently in response to the higher pulse frequencies. In the remaining 2 cases, the effective pulse-frequency range extended only to 28 pps. The trade-off between pulse frequency and pulse duration suggests that the intensity of the rewarding effect subserving optical ICSS depends on the aggregate rate of induced firing in the DA neurons, which plateaus at a rate that may depend on opsin expression. These data provide a foundation for describing the growth of reward intensity as a function of DA firing and for modelling brain reward circuitry.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.05/W29

Topic: G.02. Motivation

Support: NSERC Grant RGPIN-2016-06703

Title: Questioning the role of phasic dopamine signaling in reinforcement learning

Authors: *F. CARTER, V. PALLIKARAS, P. SHIZGAL;
Psychology / CSBN, Concordia Univ., Montreal, QC, Canada

Abstract: According to an enormously influential hypothesis, reward-prediction errors (RPEs), encoded in the firing of dopamine (DA) neurons, determine reward expectations and action values. RPEs arise from discrepancies between experienced and predicted outcomes. As learning progresses, the RPEs "predict themselves away," diminishing progressively as reward forecasts and action proclivities converge on optimal values. Abundant correlational evidence is consistent with this "RPE-DA" hypothesis, and there is supporting causal evidence from associative-conditioning studies. Here, we present operant-conditioning data that challenge the RPE-DA hypothesis. Viral transfection and Cre-lox recombination were used to express Channelrhodopsin-2 (ChR2) in midbrain DA neurons of male TH-Cre rats. A chronically implanted optical fiber was aimed at the ventral tegmental area (VTA). Depressing a lever for a

cumulative time of 2 s triggered a 1 s train of 31.6 mW, 462 nm, 5 ms optical pulses. The 4-min trials were grouped in 15 repeating triads per session. The optical reward was strong (high optical pulse frequency) on the leading trial of a triad and weak on the trailing trial. On the middle trial, reward strength was determined randomly to be either weak, moderate, or strong. The diameter of the optical probe (300 um) is ~10x larger than a DA soma, and ChR2 is found throughout the electrically excitable compartments of the neuron. Thus, DA neurons near the tip should be fired unconditionally by the optical pulses, as voltammetric data attest. The RPE-DA hypothesis predicts that over repeated trials, such unconditional DA bursts will ineluctably increment, and eventually saturate, synaptic weights subserving reward prediction and reward-seeking actions. If so, performance for optical rewards of intermediate strength must increase progressively until its maximum is attained. In contrast, we found that performance for the moderate reward on the middle trials was non-maximal and either stable or decreasing. Moreover, performance differed in two additional ways from what is typical of the model-free, temporal-difference learning originally posited by the RPE-DA hypothesis: 1) response latencies prior to receipt of the first reward on a trial show that the rats could predict the position of the trial in the triad, and 2) performance adjusted abruptly once the strength of the reward on the middle trials was revealed. Thus, specific activation of DA neurons in the absence of cues can drive learning about the sequence of environmental states, and receipt of disambiguating information produces immediate behavioral change, as in model-based learning.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.06/W30

Topic: G.02. Motivation

Support: NSERC Grant RGPIN-2016-06703

Title: The trade-off between optical power and pulse duration in optical excitation of midbrain dopamine neurons

Authors: *V. PALLIKARAS[1], F. CARTER[1], D. VELAZQUEZ-MARTINEZ[2], A. ARVANITOGIANNIS[1], P. SHIZGAL[1];
[1]Psychology / CSBN, Concordia Univ., Montreal, QC, Canada; [2]Dept. de Psicofisiologia, Univ. Nacional Autonoma De Mexico., Mexico, D.F., Mexico

Abstract: Rodents will work vigorously to deliver optical stimulation to midbrain dopamine neurons. However, many of the biophysical properties governing the optical activation of the dopamine neurons are still under investigation. We have addressed this issue by applying

psychophysical methods to characterize the interaction between optical power and pulse duration in determining the impulse flow in midbrain dopamine neurons that causes reward-seeking behaviour. The goal was to evaluate if pulse duration can effectively control the behavioural effectiveness of optical stimulation. A cre-dependent viral vector containing the transcript for Channelrhodopsin-2 was infused in the Ventral Tegmental Area (VTA) of 6 TH:Cre rats, and chronically implanted optical probes were anchored above the VTA. Stimulation was delivered at a frequency of 40 pulses per second in 1s trains. Subjects were trained to hold down a lever for 2 s to receive the optical reward. We measured time allocation (TA), the proportion of total trial time allocated to work during each trial. Sessions consisted of 10 pulse duration sweeps each consisting of 10 50 s trials. Trials were 50 s in duration, and the ITI was 10 s. The pulse duration was fixed within trials and stepped downwards in eight equal proportional steps from trial 2 to trial 10 of each sweep; trial 1 was a warm-up trial offering the same pulse duration as trial 2. The range of pulse durations tested was customized for each rat. Five sessions were run at each of a series of powers, ranging from 10 to 50 mW. TA grew in a sigmoidal fashion as pulse duration increased. If the rewarding effect depends on the aggregate rate of induced firing in the dopamine neurons, each level of TA reflects the firing of a corresponding number of dopamine neurons. If so, the lateral position of the TA-vs-pulse-duration curves across different powers reflects the trade-off between power and pulse duration in determining the size of the population of excited dopamine neurons. As expected, the TA-vs-pulse-duration curves shifted leftward over some portion of the range of optical powers. This implies that manipulation of the pulse duration can control the intensity of the optically induced rewarding effect and serve to estimate critical properties of the dopamine neurons, such as their firing fidelity as a function of optical stimulation pulse frequency.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

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Topic: G.02. Motivation

Support: ERC Starting Grant to I.W. (ERC-2014-STG 638013)
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Title: Evolution of phasic dopamine release in limbic, associative, and sensorimotor domains of the striatum during the development of habitual reward seeking

Authors: *W. VAN ELZELINGEN[1,2], W. E. BASTET[1], J. M. MATOS[1], D. SMULDERS[1], I. WILLUHN[1,2];

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Abstract: Goal-directed behavior that reliably results in desired outcomes is often automated and executed habitually after repeated performance. Evidence suggests that this switch in behavioral strategy may be paralleled by a shift in dopamine efflux from the limbic, ventromedial striatum (VMS) to the sensorimotor, dorsolateral striatum (DLS). Other work implicates a competitive interplay between DLS and the associative, dorsomedial striatum (DMS), which is associated with goal-directed behavior. Thus, we used fast-scan cyclic voltammetry (FSCV) in freely-moving rats to investigate how dopamine signaling in VMS, DMS, and DLS evolves during the development of habitual reward seeking. Male Long-Evans rats were conditioned to seek food pellets on a chained seeking-taking reinforcement schedule in an operant box. Pressing the seeking lever (distal operandum) under a VI60 schedule provided access to a taking lever (proximal operandum). Subsequent responding on the taking lever under a FR1 schedule resulted in the delivery of a food pellet. Over the progression of behavioral training, different probe tests were performed to assess how habitual the animals responded for food. FSCV measurements were conducted repeatedly throughout training to detect changes in dopamine release during habit development. Our results demonstrate no difference in task-relevant dopamine release in VMS between habitual and non-habitual states, based on comparison of early and late training time points, as well as comparisons between rats that became habitual and rats that remained non-habitual. In contrast, animals that developed seeking habits exhibited differences in both DMS and DLS dopamine that were already apparent early in training. Habits were associated with more pronounced dopamine release during distal responses (seeking lever) and decreased signaling during proximal responses (taking lever). In addition, we found decreased dopamine reactivity to unpredicted reward delivery in DLS of habitual rats, but not in DMS. Taken together, our findings do not support the hypothesis of a dopamine shift between striatal domains during habit formation, but surprisingly indicate that differential dopamine signaling in DMS and DLS is pre-existent or is recruited prior to habit formation.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

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Topic: G.02. Motivation

Support: ERC Starting Grant to I.W. (ERC-2014-STG 638013)

NWO VIDI grant to I.W. (864.14.010, 2015/06367/ALW)

Title: Differences in phasic dopamine release during Pavlovian and operant conditioning in ventromedial and ventrolateral striatum

Authors: *J. N. GOEDHOOP[1,2], I. WILLUHN[1,2];
[1]Netherlands Inst. For Neuroscience, Royal Netherlands Acad. of Arts and Sci., Amsterdam, Netherlands; [2]Dept. of Psychiatry, Amsterdam UMC, Univ. of Amsterdam, Amsterdam, Netherlands

Abstract: Dopamine neurons are known for their responses to rewarding events and their predictors. However, the precise information conveyed by dopamine signals (e.g., reward prediction error, value, motivation, or movement) and their regional specificity are under active debate. The striatum receives the largest projection from dopamine neurons and consists of functional domains that are defined by their afferents. The ventromedial striatum (VMS) receives predominantly limbic input and the ventrolateral striatum (VLS) mainly input from the insula cortex. To further characterize dopamine signaling in VMS and VLS, we directly compared Pavlovian and operant conditioning and systematically varied several task parameters.
Adult, male Long-Evans rats (n = 18) with chronically implanted electrodes for fast-scan cyclic voltammetry (FSCV) in VMS and VLS were trained on either an appetitive Pavlovian or instrumental conditioning paradigm in which a conditioned stimulus (CS) predicted the delivery of a reward or the opportunity to execute an action to obtain a reward. Task conditions were kept the same with the exception of the operant-lever response requirement.
We observed differences in VMS dopamine release between Pavlovian and instrumental conditioning during presentation of either CS or unconditioned stimulus (US). Specifically, in addition to reward prediction, VMS dopamine appeared to encode the anticipation to execute the operant action, characterized by sustained release during CS presentation until lever press. In VLS, we observed overall smaller CS- and US-induced dopamine, an incomplete transfer of dopamine from US to CS during Pavlovian conditioning, and a lack of a sustained CS response in instrumental conditioning.
Our results demonstrate that dopamine release induced by reward presentation and its CS predictor is region-specific, differing in size and signal allocation between VMS and VLS. In addition, our findings suggests that, specifically in VMS, dopamine signals convey not only information consistent with a reward prediction error or value signal, but also other information not captured by these concepts. Potentially somewhat related to motivation, it appears that dopamine release in this region is also shaped by the anticipation to perform a rewarding action.

Disclosures: **J.N. Goedhoop:** None. **I. Willuhn:** None.

Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.09/W33

Topic: G.02. Motivation

Support: CONACYT Grant 255317
CONACYT Grant 582196

Title: Nutritional programming during pregnancy and lactation sensitizes food addiction like behavior in offspring of rats

Authors: *L. MONTALVO MARTINEZ[1], G. CRUZ CARRILLO[1], L. FUENTES MERA[1], R. ORTIZ LÓPEZ[2], A. CAMACHO MORALES[1];
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Abstract: Obesity associates to excessive hypercaloric food intake leading to increase in body mass index. Incentive motivation to hypercaloric foods is partly related to an addictive like behavior phenotype. Addiction correlates with selective changes in gene expression in specific brain reward regions, including the Nucleus Accumbens (NAc), which might be potentially transmitted to the offspring by transgenerational inheritance. Here, we used a murine model of maternal nutritional programming to determine whether: 1) addiction like behavior of mothers is transmitted to male offspring (F1), and 2) candidate genes for food addiction in the NAc of addicted F1, correlates to aberrant synaptic plasticity gene profile found in drug addiction. We used 9 groups of Wistar rats (8-10 weeks), including 2 groups of females (F0) exposed for 9 weeks (premating, pregnancy and lactation) to hypercaloric diet (HD) or control diet (CD). All groups were trained by operant conditioning protocols (FR1, FR5, PR, 12 days) using a Skinner type box, following by chocolate pellets as a reward to determine its addiction like behavior. Microarray analysis from the NAcshell of the offspring was performed to identify candidate genes. Our results show that F0 females fed with CD exhibit an enhanced motivation to hypercaloric rewards compared to F0 females fed HD. Nevertheless, addiction like behavior from F0 females fed HD was efficiently transmitted to the F1 offspring in compare to F0 females fed CD. Likewise, global expression microarrays analysis showed that addiction like behavior subjects exhibit alteration in the expression of several genes involved in drug addiction such as: DR2, GluA1, GluA2, GluA3, BDNF, CREB, FosB, SIRT1, HDAC1, MEF2. Genomic interaction pathways demonstrated interactive nodes involved in synaptic plasticity and neuronal function. Our results demonstrate that maternal hypercaloric programming sets food addiction like behavior susceptibility which positively is transmitted to male offspring showing selective gene expression changes in NAc shares during drug addiction phenotype.

Disclosures: **L. Montalvo Martinez:** None. **G. Cruz Carrillo:** None. **L. Fuentes Mera:** None. **R. Ortiz López:** None. **A. Camacho Morales:** None.

Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

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Topic: G.02. Motivation

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NIH Grant DP1 AT009925
NIH Grant DP2 DK102256
NIH Grant R01 MH102441
NIH Grant R01 MH115920

Title: Cholinergic basal forebrain neurons can drive motivated behavior by serving as a conditioned stimulus

Authors: *E. Y. KIMCHI[1,2], A. BURGOS-ROBLES[2], G. A. MATTHEWS[2], T. L. CHAKOMA[2], M. PATARINO[2], J. C. WEDDINGTON[2], W. YANG[2], R. SIMONS[2], S. FOUTCH[2], M.-F. FONG[2], M. F. BEAR[2], K. M. TYE[3];
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Abstract: During motivated behavior, subjects actively interpret external cues to determine whether to seek rewards or avoid punishments. Basal forebrain cholinergic circuits are thought to modulate how neural circuits process these cues, either by increasing attention to specific sensory stimuli or by augmenting the effects of reinforcers on learning and memory. Less is known, however, regarding whether phasic activation of basal forebrain cholinergic neurons impacts motivated behavior even in the absence of other cues. We trained head-fixed ChAT::cre mice to lick to collect fluid rewards. Phasic optogenetic stimulation of nucleus basalis cholinergic neurons triggered reward collection, even prior to training with other sensory stimuli (ChR2 n=17, eYFP n=10, linear mixed effects model p = 0.025). Mice expressing ChR2 in cholinergic neurons initiated licking after photostimulation with a median lick latency of 427ms (n=17, interquartile range 207-682ms) as compared to a median lick latency of 991 ms in eYFP mice (n=10, interquartile range 754-1036ms; signrank p = 0.006). Licking after cholinergic stimulation was dependent on pairing with reward; phasic cholinergic stimulation that was not paired with reward did not trigger reward collection (ChR2 n=17, eYFP n=10, linear mixed effects model p = 0.834). The effects of phasic cholinergic stimulation on reward collection were impaired by an antagonist of muscarinic cholinergic receptors (intraperitoneal scopolamine, 0.3 mg/kg, vs. saline, n=6, signrank p = 0.031), but not nicotinic cholinergic receptors

(intraperitoneal mecamylamine, 1 mg/kg, vs. saline, n=6, signrank p=0.188). Similar increases in reward collection behavior were seen with photostimulation of cholinergic terminals in the basolateral amygdala (ChR2 n=8, eYFP n=4, linear mixed effects model p=0.017). Preliminary results suggest that photoactivation of cholinergic terminals in the basolateral amygdala suppressed neural activity, both in vivo and ex vivo. Preliminary analysis of ex vivo recordings suggest that basolateral amygdala projection neurons were monosynaptically inhibited via muscarinic receptors, whereas GABAergic neurons were monosynaptically excited via nicotinic receptors. These results reveal a novel mode of action for basal forebrain cholinergic neurons, suggesting that phasic cholinergic activation can impact motivated behavior with subsecond precision via muscarinic receptors, even in the absence of other cues. Basal forebrain cholinergic neurons therefore may not only amplify neural processing or plasticity of sensory stimuli, but also may function as conditioned stimuli in and of themselves.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.11/W35

Topic: G.02. Motivation

Support: R01-MH115920-01
DP1-AT009925-01
R01-MH102441-03
DP2-DK-102256-03

Title: Amygdalostriatal transition zone circuits mediating associative learning and motivated behaviors

Authors: ***F. MILLS**[1], H. S. CHEN[2], S. SHAO[1], M. E. LEMIEUX[1], C. R. LEE[3], K. M. TYE[1]; [1]The Salk Inst. for Biol. Studies, La Jolla, CA; [2]MIT, Cambridge, MA; [3]Univ. of California San Diego, La Jolla, CA

Abstract: The ability to respond appropriately to stimuli that predict rewards or punishments lies at the core of evolutionary fitness, and is disrupted in a number of neuropsychiatric disease states. Although relatively unexplored, the amygdalostriatal transition zone (ASt) may play a crucial role in parallel with the amygdala in mediating associative learning and behavioral responses to salient stimuli. Like the amygdala, the ASt receives converging input from two major streams of sensory information, the thalamic and cortical pathways. However, the

downstream projections of the ASt are distinct from the canonical outputs of the amygdala complex, and are integrated with striatal circuits involved in action selection. Despite this intriguing circuit connectivity, the function of the ASt is almost completely unknown, resulting in a major gap in our knowledge of circuits underlying motivated behaviors. In the present study, our data show that optogenetic activation of the ASt is sufficient to produce aversive behavioral responses. Unilateral activation of ChR2-expressing neurons in the ASt drives robust freezing behavior (83% increase in ChR2 group vs. -2% in eYFP controls; p=0.0015, unpaired t-test) and real-time place avoidance of areas paired with ASt stimulation (32% reduction of time in 'ON'side vs. eYFP controls during last 10 min; p=0.012 unpaired t-test. N=8 mice ChR2, 10 mice eYFP). Additionally, using *in vivo* electrophysiology and optogenetic-mediated 'phototagging' we identify distinct populations of ASt neurons that encode opposing conditioned responses to cues predicting rewarding and aversive stimuli (N=6 mice, n=31 neurons). Finally, in loss-of-function experiments we find that optogenetic inhibition of a subpopulation of ASt neurons causes a striking reduction in conditioned fear responses to a shock-predicting cue (51% decrease in freezing, p=0.00086, paired t-test, N=6 mice NpHR, n=8 mice eYFP). Consequently, we believe that the ASt may be an overlooked and critical structure in mediating responses to conditioned stimuli, and may also contribute to behaviors which have traditionally been attributed to canonical amygdala circuits.

Disclosures: F. Mills: None. **H.S. Chen:** None. **S. Shao:** None. **M.E. Lemieux:** None. **C.R. Lee:** None. **K.M. Tye:** None.

Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

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Topic: G.02. Motivation

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Postdoctoral Fellowship from MIT Simons Center for the Social Brain
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R01-MH102441-03
DP2-DK-102256-03

Title: Wireless recording of projection-defined PFC neurons during a novel social dominance task

Authors: *N. PADILLA-COREANO[1], J. C. WEDDINGTON[2], R. ZHANG[2], R. R. ROCK[2], C. CHANG[2], S. B. HAUSMANN[1], G. MATTHEWS[2], J. P. CURLEY[3], K. M. TYE[1];
[1]The Salk Inst., La Jolla, CA; [2]Massachussetts Inst. of Technol., Cambridge, MA; [3]Psychology, Univ. of Texas at Austin, Austin, TX

Abstract: Both humans and mice live in groups organized by social hierarchies. By adjusting behavior based on their social rank, animals decrease unnecessary aggression and save energy. Although hierarchies are central to successful group dynamics, the neural basis of dominance behaviors remains poorly understood. Cross-species evidence suggests that the medial prefrontal cortex (mPFC) is crucial for social dominance behaviors (Wang et al., 2011, Zhou et al., 2017, Zink et al., 2008). Given the role of the lateral hypothalamus (LH) in homeostatic functions, and its connectivity with the mPFC, it is well-positioned to help modulate social behaviors in a rank-dependent manner. Considering that dominant animals typically exercise priority access to resources, we designed a novel behavioral task, the “reward competition assay”. This assay utilizes a trial structure to facilitate statistical comparisons wherein mice compete for a reward that is signaled by a tone. Mice were food restricted and trained to associate a tone with a palatable reward (Ensure). Once mice learned the task, they were paired with a cage mate to compete for the reward. To validate this task, we ranked mice using the tube test (Wang et al., 2011) and tested them on the reward competition assay. Across the session, dominant mice (as defined by tube rank) won more rewards than subordinates, as the percent of rewards obtained for the dominant mice was higher (paired t-test; % rewards subordinate vs dominant $p<0.01$; n=12). Using this novel reward competition assay we investigated the role of mPFC->LH projectors in social dominance. Our preliminary data show that optogenetic stimulation of the mPFC->LH projectors increased winning in subordinate mice (paired t-test; % rewards obtained OFF vs ON sessions $p=0.0047$; n=5). However, we saw no effects of stimulation when mice were performing the reward task alone, indicating that mPFC->LH projectors modulate social competition for a reward, but not reward-seeking behavior. Furthermore, we used wireless electrophysiology to investigate how mPFC activity relates to social dominance during the reward competition assay. We recorded mPFC single units in both dominant and subordinate mice (n=4) while they competed for Ensure rewards. Preliminary data suggest that mPFC single units represent competition as they fired differentially in trials when there were high vs low levels of competition for the reward (n=74 single units recorded). We hypothesize that these “competition cells" in the mPFC may project to the LH in order to inform social homeostatic circuits and integrate these signals with other homeostatic systems such as those regulating energy balance (hunger).

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.13/W37

Topic: G.02. Motivation

Support: NSF DGE-1746891
NIH T32 NS91018-17
NARSAD Young Investigator Award
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NIH R01 DA035943

Title: Ventral pallidum neurons signal reward prediction errors consistent with reinforcement learning

Authors: *D. J. OTTENHEIMER[1], B. A. BARI[1], E. SUTLIEF[1], J. M. RICHARD[4], J. Y. COHEN[1,2], P. H. JANAK[1,2,3];
[1]Solomon H Snyder Dept. of Neurosci., [2]Kavli Neurosci. Discovery Inst., [3]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD; [4]Dept. of Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: With connections to the nucleus accumbens (NAc) and the ventral tegmental area (VTA), the ventral pallidum (VP) is well positioned to contribute to reward-related computations. To characterize value signaling in this circuit, we implemented a behavioral task where rats received on randomly interspersed trials signaled presentations of 110 μl of either 10% sucrose or 10% maltodextrin solutions. We previously reported that the activity of neurons in both regions reflected the rats' preference for sucrose; notably, a greater proportion of neurons in VP were reward selective, and their activity preceded that of NAc neurons, a surprising result given the canonical role of VP as a major output of NAc (Ottenheimer et al., 2018). Despite no requirement that the rats predict the upcoming choice, and no behavioral differences across trial types, we noted a prominent influence of previous outcome on VP reward-evoked activity. To examine this further, here we employed a linear regression approach that previously revealed an exponentially-weighted impact of multiple previous trials on dopamine neuron activity (Bayer and Glimcher, 2005). We similarly found exponential dependence of VP activity on reward history. Prompted by this result, we classified neurons in VP and NAc as RPE-encoding in an unbiased manner using maximum likelihood estimation of a standard reinforcement learning model; this approach confirmed a larger proportion of RPE-encoding cells in VP. We further tested the adherence of VP neuronal activity to RPE in two additional tasks. First, in sessions where sucrose and maltodextrin were presented consecutively in two blocks of 30 trials each, we observed an exponential decay of the sucrose-evoked signal, consistent with an exponential weighting of previous outcomes; moreover, this led to fewer reward-selective neurons and the emergence of predictive anticipatory firing. Next, in sessions with where on some trials the identity of the outcome was indicated by a predictive cue, we found that neuronal signaling integrated both trial history and cued information. Our work emphasizes the robustness of RPE-like value signaling in VP and encourages further consideration of the contributions of VP to reinforcement learning.

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Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

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Topic: G.02. Motivation

Support: NIH Grant DA035943
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Title: Amygdalocortical circuits for the dynamic regulation of conditioned reward-seeking

Authors: *K. M. FRASER, P. H. JANAK;
Johns Hopkins Univ., Baltimore, MD

Abstract: While much is known about the ability of cues in the environment to serve as predictors of reward, the psychological and neurobiological mechanisms that regulate the predictive and motivational significance of reward-paired cues remains unclear. We investigated the regulation of conditioned reward seeking by discrete and phasic sensory events in the environment that inform whether a traditional conditioned stimulus will or will not be followed by reward delivery by making use of an occasion setting procedure. To assess potential neural circuits underlying occasion setting we trained male Long-Evans rats in a task in which a conditioned stimulus was followed by sucrose reward only if preceded in time by the presentation of a different occasion setting cue. Presentation of either the occasion setting cue or the conditioned stimulus on their own was not followed by reward. As a result of this contingency, conditioned responding to the food cup was highest to the conditioned stimulus when preceded by the occasion setting cue. Using reversible inactivation with the GABA agonists baclofen and muscimol, we found that inactivation of either the basolateral amygdala (BLA) or orbitofrontal cortex (OFC) prevented rats from using occasion setters to produce adaptive conditioned reward seeking. We then recorded BLA and OFC neurons in well-trained rats and found that BLA neurons exhibit a greater excitation to the conditioned stimulus when it was preceded by its occasion setter than on trials when it was presented in isolation. We next assessed the contributions of amygdalocortical connections by selectively expressing the inhibitory DREADD in either BLA to OFC or OFC to BLA neurons. Inhibition of OFC to BLA projections, but not BLA to OFC projections, moderately disrupted the ability of rats to use the occasion setter to guide their reward-seeking. These results are consistent with state value encoding theories of the BLA and OFC and suggest activity within this circuit is critical for flexibly updating the motivational significance of cues on a moment-to-moment basis.

Disclosures: K.M. Fraser: None. **P.H. Janak:** None.

Poster

506. Mechanisms Underlying Decision-Making, Motivation, and Reinforcement

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 506.15/W39

Topic: G.02. Motivation

Support: R01AA026306

Title: Ventral hippocampus, basolateral amygdala, and nucleus accumbens inactivation impairs cue responding in Pavlovian-conditioned contextual discrimination

Authors: *T. KIM[1], P. JANAK[1,2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: In order to understand the role of environmental contexts in relapse, we and others have used ABA designs to show that exposure to previously rewarded cues in a previously rewarded context can elicit renewal of conditioned responding even in the absence of reward. However, in these experiments, it is not yet clear if renewal is driven by the conditioned properties of cue, the context, or by modulation of cue responding by the context. To address this question, we used a biconditional contextual discrimination task in which male Long Evans rats had to rely on contextual cues in the chambers to determine which of the two cues was paired with reward that day. We examined if the ventral hippocampus (vHPC), dorsal hippocampus (dHPC), basolateral amygdala (BLA), and nucleus accumbens shell (NAcSh) were necessary for this behavior. Rats were trained in context A to discriminate among four auditory cues: a CS^+ that was followed by a 20% sucrose (20S) reward, a CS^- that was followed by nothing, a CSA^+ that was followed by 20S, and a CSA^- followed by nothing. Rats were then placed into context B where the meanings of the CS^+ and CS^- from context A were switched such that the CS^- cue was now rewarded and the CS^+ cue was not. The meaning of the CSA^+ and CSA^- remained constant between the two contexts. The two contexts differed in scent, chamber wall color, and floor texture. Once rats learned the switching CS^+ and CS^- cues in both contexts, they were tested under extinction in both contexts where all four cues were presented but no reward was delivered. Before each test, rats were administered an infusion of either saline or a mixture of muscimol and baclofen into the dHPC, vHPC, NAcSh, or BLA. Inactivation of the vHPC, BLA, and NAcSh reduced responding to all four cues regardless of the context, although the ability to discriminate among rewarded and unrewarded cues remained intact, perhaps suggesting a decrease in motivation.
Decreased responding was specific to cue related behaviors as inactivation of these regions did not cause a locomotor deficit. Inactivation of the dHPC had no effect on responding. These results demonstrate that none of these four brain regions alone is necessary for rats to use these contextual stimuli to determine the currently rewarded cue.

Disclosures: **T. Kim:** None. **P. Janak:** None.

Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.01/W40

Topic: G.02. Motivation

Title: Aggression alters mood-related behavior in adult sexually experienced male CD-1 mice

Authors: *A. THEMANN, O. LIRA, F. J. FLORES-RAMIREZ, S. D. IÑIGUEZ;
Dept. of Psychology, The Univ. of Texas at El Paso, El Paso, TX

Abstract: Maladaptive aggressive behavior has been linked to a wide array of psychiatric disorders including autism, antisocial personality disorder, and schizophrenia. Although the relationship between maladaptive aggression and psychiatric dysfunction is not well understood, recent evidence indicates that aggressive displays towards conspecifics may be perceived as rewarding - and that this hedonic experience may elicit a similar response as other rewarding stimuli, including food, sex, and drugs of abuse. Nevertheless, the relationship between aggression and mood-related illnesses has not been thoroughly investigated using preclinical affect-related models. To address this issue, we examined whether displays of aggressive behavior result in changes in sensitivity to the rewarding properties of sucrose and novel environments, as well as responses to inescapable stress situations. Specifically, male (retired breeder) CD-1 mice were subdivided into aggressive (AGG) and non-aggressive (NON-AGG) groups, based on their latency to attack an intruder mouse into their homecage, during a three-day screening paradigm. Mice were considered AGG if they displayed attack latencies below 10 sec across the three screening days, while animals with attack latencies greater than 30 sec (or not attacking at all) were classified as NON-AGG. One hour after aggression screening (day 3), responsivity to the sucrose (1%) preference, open field, elevated plus maze, and the tail suspension tests were conducted in separate groups of experimental mice. We found that AGG mice display an increased preference for a 1% sucrose solution, as well as increased exploration in novel environments, per the elevated plus-maze and open field tests. In addition, AGG mice showed reduced immobility in the tail suspension test, representative of a resilient-like behavioral response. Collectively, our data suggest that aggression modulates behavioral sensitivity on preclinical models for the study of mood-related illnesses.

Disclosures: **A. Themann:** None. **O. Lira:** None. **F.J. Flores-Ramirez:** None. **S.D. Iñiguez:** None.

Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.02/W41

Topic: G.02. Motivation

Title: Vicarious social defeat stress induces depression-related outcomes in a sex-specific manner in adolescent C57BL/6 mice

Authors: *M. RODRIGUEZ, E. J. FLORES, S. INIGUEZ;
Dept. of Psychology, The Univ. of Texas At El Paso, El Paso, TX

Abstract: Major depression disorder (MDD) is a prevalent illness that negatively affects the adolescent population, with females having a higher likelihood of diagnosis. Stress is a well-recognized risk factor for the development of MDD, in which psychological stress, in particular, plays a role in the etiology of mood-related disorders. Although there has been progress in our understanding of how animal models of psychological stress induce depression-related phenotypes, a prevailing limitation is that most of this work has been conducted mostly in adult males. Thus, to examine this issue at the preclinical level, we adopted the vicarious social defeat stress (VSDS) paradigm to assess whether psychological stress induces depression-related outcomes in adolescent mice. Specifically, postnatal day (PD) 35 male and female C57BL/6 mice vicariously experienced the defeat bout of a male conspecific, by a larger male CD1 aggressor for 10 consecutive days (10 minutes per day). Twenty-four hours after the last day of VSDS exposure (i.e., PD45), separate cohorts of experimental mice were tested on the social interaction, tail suspension, and light/dark box tests. The results indicate that when compared to non-stressed controls, VSDS exposed male mice displayed a depressive-like phenotype per significant increases in avoidance behavior and immobility on the tail suspension test. Furthermore, VSDS male mice displayed an anxiogenic-like phenotype, since they spent less time in the lighted compartment of the light/dark box, along with significant decreases in body weight. Conversely, in adolescent females, VSDS did not influence performance in any of the behavioral tasks assessed. These findings indicate that adolescent VSDS exposure induces depression-related behavior in a sex-specific manner in C57BL/6 mice.

Disclosures: M. Rodriguez: None. **E.J. Flores:** None. **S. Iniguez:** None.

Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.03/W42

Topic: G.02. Motivation

Title: Upregulation of hippocampal extracellular signal-regulated kinase (ERK)-2 induces antidepressant-like behavior in the rat forced swim test

Authors: *I. GARCIA-CARACHURE, F. J. FLORES-RAMIREZ, S. D. IÑIGUEZ; Psychlogy, The Univ. of Texas at El Paso, El Paso, TX

Abstract: The hippocampus mediates responses to affect-related behavior in preclinical models of pharmacological antidepressant efficacy, such as the forced swim test. However, the molecular mechanisms that regulate escape-directed behavior in this preclinical model of despair are not well understood. Here, using viral-mediated gene transfer, we assessed how overexpression of extracellular signal-regulated protein kinase (ERK)-2 within the dorsal hippocampus influenced behavioral reactivity to inescapable swimming stress in adult male Sprague-Dawley rats. When compared to controls, rats overexpressing hippocampal ERK-2 displayed increases in the time to initially adopt a posture of immobility, along with decreases in total time spent immobile, without influencing general locomotor activity. Collectively, the results indicate that hippocampal upregulation of ERK-2 increases escape-directed behavior in the rat forced swim test, thus providing insight into the neurobiological mechanisms that mediate antidepressant efficacy.

Disclosures: I. Garcia-Carachure: None. **F.J. Flores-Ramirez:** None. **S.D. Iñiguez:** None.

Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.04/W43

Topic: G.02. Motivation

Title: The enduring anxiogenic phenotype induced by juvenile antidepressant exposure is ameliorated by fluoxetine re-exposure in adult female C57BL/6 mice

Authors: *F. J. FLORES-RAMIREZ, O. LIRA, F. D. RODRIGUEZ, J. PRECIADO-PIÑA, D. I. PARDO, S. A. CASTILLO, S. D. INIGUEZ;
Psychology, Univ. of Texas at El Paso, El Paso, TX

Abstract: Accumulating preclinical evidence indicates that adolescent exposure to antidepressant medications results in altered behavioral responses to stress in adulthood. However, to date, these preclinical experimental approaches have been conducted primarily using male subjects. This is surprising given that females, when compared to males, are more likely to be diagnosed with mood-related disorders, and thus, be prescribed to antidepressant medications. Therefore, to examine if altered sensitivity to anxiety-inducing situations are exhibited in adulthood, as a result of juvenile exposure to antidepressants, we exposed adolescent female C57BL/6 mice to the selective serotonin reuptake inhibitor (SSRI) fluoxetine (FLX). Specifically, female mice were forced to consume FLX in their drinking water (250 mg/l) from postnatal day [PD]-35 to PD49, and later assessed in adulthood (PD70+) on responsivity to the elevated plus-maze (EPM) and the light-dark box (LDB) tests - behavioral paradigms commonly used to assess anxiety-like responses in rodents. Our results show that adult female mice pretreated with FLX during adolescence spent less time in the open arms of the EPM, when compared to saline-pretreated controls. Similarly, when tested on the LDB, FLX-pretreated mice displayed significantly longer latencies (sec) to enter the light-side compartment of the testing chamber, and spent significantly less time (sec) within it, when compared to controls. To evaluate whether FLX re-exposure would reverse the SSRI-induced anxiogenic phenotype in adulthood, we reinstated SSRI treatment from PD70-84, and evaluated responses on the EPM and LDB. Interestingly, we found that adult re-exposure to FLX reversed the enduring anxiogenic phenotype, per the EPM and LDB paradigms. Collectively, our data suggest that adolescent exposure to FLX mediates behavioral adaptations that endure into adulthood, which are indicative of a generalized anxiogenic-like phenotype, and that this effect is ameliorated by reinstatement of FLX treatment later in life.

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Poster

507. Stress, Anxiety, and Aversion

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Topic: G.02. Motivation

Support: UL1GM118979
TL4GM118980
RL5GM118978

Title: Adolescent rats exhibit context-dependent methamphetamine sensitization while adult rats fail to exhibit sensitization using a one-trial procedure

Authors: *B. W. SORTMAN[1], C. MORENO-BARRIGA[1], D. FRANCO[1], E. NUNEZ[1], K. J. THIEL[2], A. R. ZAVALA[1];
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Abstract: Sensitization is a well-known effect of psychostimulant drugs such as cocaine, amphetamine, and methamphetamine and is characterized as a leftward shift in the dose-response curve. In rodents, sensitization is manifested as an enhanced behavioral response after a single injection (one-trial) or repeated (multi-trial) administration of the drug. One-trial behavioral sensitization is exhibited differently across ontogeny. Specifically, preweanling rats show context-independent one-trial behavioral sensitization to cocaine (i.e., sensitization is evident regardless of where cocaine is given), while adult rodents show context-dependent sensitization (i.e., sensitization is evident only in the context where cocaine was given previously). Interestingly, adolescent rats do not show one-trial sensitization to cocaine or methamphetamine. The present study sought to examine further the development of one-trial methamphetamine sensitization in adolescent (i.e., postnatal day (PD) 39) and adult (PD 69) rats using low doses of methamphetamine, as well as to determine the role of context in moderating a sensitized response. Male and female rats (PD 38 or 68) were injected with either saline or methamphetamine (3.0 mg/kg, IP) in their home cage (home-paired) or an activity chamber (activity-paired). The following day (i.e., PD 39 or 69), rats received a challenge injection of methamphetamine (0.1-1.0 mg/kg, IP) in the activity chamber and their locomotor activity was assessed for 90 min. A separate control group received saline on (PD 38 or 68), and received a saline challenge injection the following day (PD 39 or 69). In contrast to previous findings, adolescent rats showed context-dependent one-trial behavioral sensitization to methamphetamine (0.3 mg/kg). Moreover, adult rats failed to show behavioral sensitization to any dose of methamphetamine. This data suggests that adolescent rats show increased sensitivity to methamphetamine compared to adult rats. This data is consistent with prior studies demonstrating that adolescent rats are more sensitive to the behavioral effects of methamphetamine compared to adult rats (e.g., enhanced conditioned place preference and self-administration of methamphetamine). The ontogenetic differences in behavioral sensitization highlights the need to examine further the mechanisms underlying these developmental differences.

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Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.06/X1

Topic: G.03. Emotion

Title: Lateral habenula gabaergic cells: Involvement in anxiety and stress-related behaviors

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Abstract: *Rationale:* The lateral habenula (LHb) is thought to play an important role in coordinating behavioral and physiological responses to stress. Until recently, neurons in the LHb were considered exclusively glutamatergic. However, recent evidence suggests that GABA cells are not only expressed in the LHb but that they may participate in stress-related behaviors. Here, we sought to study the connectivity, activity, and functions of GABA neurons in LHb of mice. *Methods:* Using Vgat/TdTomato mice, we described the location of a subset of LHb GABA cells. Then, using VGAT-Cre mice and viral tracers, we mapped the inputs/outputs of these GABA cells. We assessed, using fiber photometry, the activity of these cells in response to aversive (foot-shocks, tail pinch) or rewarding (sucrose) stimuli. Finally, we chemogenetically manipulated the activity of these cells in aversive and conflict-based behavioral tasks. *Results:* We provided strong evidence that functional GABAergic cells are contained within the LHb. These cells receive inputs from a more restricted connectome than LHb glutamatergic cells. For instance, they do not receive inputs from the entopeduncular nucleus, considered one of the major sources of LHb inputs. In regard to their function, chemogenetic manipulation of these LHb GABAergic cells induced anxiety-like behaviors and impacted decision-making processes, suggesting an important role in regulating mood and cognition. *Conclusions:* Small populations of GABAergic neurons in the habenula play an important role in signaling aversive behavioral states. These cells may participate in behavioral adaptation upon stressful situations. Further work on these GABA cells will help to better define the cellular mechanisms by which the habenula regulates behavior. **Keywords:** Lateral habenula, GABA, tracing, fiber photometry, anxiety, stress, decision making

Disclosures: V. Mathis: None. **P.J. Kenny:** None.

Poster

507. Stress, Anxiety, and Aversion

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Topic: G.03. Emotion

Support: NRF Grant 2016R1C1B2007319
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Title: The role of septal enkephalinergic neurons in anxiety

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Abstract: The lateral septum (LS), a forebrain region flanked by the lateral ventricles, is a key player in the regulation of anxiety. The LS is anatomically connected to a number of regions implicated in stress, anxiety and depression, and classic studies using lesion, electrical stimulation, pharmacological manipulations and recordings have implicated the LS in anxiety. Furthermore, recent studies have established the roles of several genetically defined septal subpopulations in anxiety using modern cell type-specific circuit dissection techniques (e.g. Anthony et al., 2014; Besnard et al., 2019). Despite the progress, the function of the many of the cell types in the LS remains largely unexplored. Notably, opioid peptides are involved in a variety of negative affective states including anxiety, and numerous studies have linked opioid neurotransmission in the LS to anxiety. However, the role of the LS neurons expressing opioid peptides in anxiety remains unexplored. Therefore, we explored the function of the LS subpopulation defined by the expression of encephalin in anxiety. Using optical recordings in freely-behaving mice, we observed that septal enkephalinergic neurons are activated by anxiogenic or stressful stimuli. We are currently examining the causal role of this population using optogenetic and chemogenetic tools. Our preliminary data suggest that septal enkephalinergic neurons can modulate diverse anxiety-related behaviors. Further experiments in other related behaviors and physiological measurements will reveal the precise role of these neurons in modulating specific anxiety state features.

Disclosures: **M. An:** None. **K. Kim:** None. **H. Kim:** None. **S. Kim:** None.

Poster

507. Stress, Anxiety, and Aversion

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NARSAD Independent Investigator Award

Title: The amygdala differentially regulates defensive behaviors evoked by CO_2

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Abstract: CO_2 inhalation provokes panic attacks in patients with panic disorder. Identifying the brain sites involved could provide important mechanistic insight into the illness. In mice, the amygdala has been suggested to promote CO_2-evoked responses; however, recent studies in humans with amygdala damage indicate the amygdala is not required for CO_2-induced fear and panic. To clarify the role of the amygdala, we produced lesions in mice paralleling the lesions in humans. Compared to sham controls, we found that amygdala-lesioned mice froze less to 10% CO_2, and unlike shams they also began to jump frenetically. At 20% CO_2, controls also exhibited jumping suggesting it is a normal response to more extreme CO_2concentrations. The effect of amygdala lesions was specific to CO_2 as amygdala-lesioned mice did not jump in response to a predator odor or to an auditory conditioned stimulus. In amygdala-lesioned mice, jumping evoked by 10% CO_2 was eliminated by co-lesioning the dorsal periaqueductal gray, a structure previously implicated in panic and escape-related behaviors. Together, these observations suggest a dual role for the amygdala in the CO_2 response: promoting CO_2-induced freezing, and opposing CO_2-induced jumping, which may help explain the exaggerated CO_2 responses in humans with amygdala lesions.

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Poster

507. Stress, Anxiety, and Aversion

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Topic: G.03. Emotion

Support: Supported by SPIN (Austrian Science Fund, FWF, W1206)

Title: Region and cell-type specific contribution of mGlu5 receptors to social behavior and anxiety

Authors: *A. RAMOS PRATS, F. FERRAGUTI;
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Abstract: A large body of evidence has implicated an altered signaling or expression of the metabotropic glutamate 5 (mGlu5) receptor in the pathology of several neuropsychiatric disorders, including autism, anxiety disorders and schizophrenia. In particular, enhanced mGlu5 receptor signaling has been suggested to underlie impaired social behavior, a symptom shared by these disorders. Recent research suggests that systemic deviations in any direction of mGlu5 receptor function may lead to social dysfunction. Whereas germ line deletion of the mGlu5 receptor gene leads to a phenotype showing remarkable analogies with Williams syndrome, characterized by a marked prosocial behavior and enhanced anxiety, increased mGlu5 receptor expression and signaling underlies obsessive-compulsive behavioral abnormalities. So far, it remains unclear how mGlu5 receptors contribute to the expression of social preference and anxiety and particularly which neural circuits underlying these behaviors are preferentially affected by activity of these receptors. Our work aims at elucidating whether mGlu5 receptor ablation in a cell-type specific manner can affect social and anxiety-like behavior. To this aim, we performed stereotactic injections of an AAV-CamKIIa-Cre-GFP viral vector in the ventral hippocampus of $mGluR5^{Fl/Fl}$ mice to selectively ablate mGlu5 receptors in that area. We then tested these mice in several classical behavioral paradigms to assess social and anxiety-like behaviors. Our preliminary data suggests that mGlu5 receptors in the ventral hippocampus modulate novelty-induced locomotion and have divergent effects on social recognition and anxiety. Our findings corroborate the view of a complex role played by mGlu5 receptors in social behavior and anxiety and questions systemic pharmacological treatment strategies aimed at alleviating social dysfunction and pathological anxiety e.g. in neurodevelopmental disorders such as autism.

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Poster

507. Stress, Anxiety, and Aversion

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Topic: G.03. Emotion

Support: CAPES-PROEX
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Title: Central inhibition of heme oxygenase carbon monoxide pathway modifies the anxiety-like behavior in endotoxemic rats

Authors: *C. R. A. LEITE-PANISSI, E. O. PRIMINI, M. C. CARVALHO;
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Abstract: The carbon monoxide (CO) is a neuromodulator gas that is produced by the action of the enzyme heme-oxygenase (HO), and it may be involved in several biological processes such as nociception and emotional modulation. This mechanism can modulate noradrenergic neurons in locus coeruleus (LC), which makes projections to neural substrates, such as hippocampus, amygdala, and hypothalamus. The presence of bacterial endotoxins (Lipopolysaccharide, LPS) in blood circulation can result in a set of adaptive behavioral changes referred to as sickness behavior, that prepare the body to cope with viral or bacterial infections. Several mechanisms may be related to central nervous system activation by the peripheral production of proinflammatory cytokines. Previous studies showed that the HO-CO pathway is involved in the regulation of anxiety in healthy animals. Thus, the project aims to evaluate if the HO-CO pathway regulates the anxiety in endotoxemic rats. Male Hannover rats (300g, n = 8 per group; CEUA (# 2017. 1.381.58.4) were anesthetized and submitted to surgery to implant a guide cannula toward to the fourth ventricle. Afterward, rats were divided into groups for the administration of LPS (200µg/kg) or sterile saline (SAL 0.9%) via i.p. and HO enzyme inhibitor, tin protoporphyrin IX (SnPP; 0.005M; 2µL) or vehicle (DMSO 10%) via i.c.v. After 2h, the rats were submitted to the emotional behavior tests, elevated plus maze (EPM) during 5 min or ultrasonic vocalization (USV) over 10 min. The fever was evaluated through the tail skin temperature (TsK) by a thermographic camera (Flir One). ANOVA one-way and two-way followed by Tukey and Bonferroni test were applied, with $p < 0.05$. The results showed a reduction of TsK after 120 min and 180 min of the LPS injection (Bonferroni test; $p < 0.001$). In EPM, LPS+VEHI group presented a decrease in the number of entries into the open arms compared to the SAL + VEHI (Tukey test; $p < 0.05$). The treatment with SnPP reversed the anxiety-like behavior partly since the LPS+SnPP group presented a higher number of heading dipping compared to LPS + VEHI (Tukey test; $p < 0.05$). Furthermore, the i.c.v. treatment with

SnPP (LPS+SnPP group) prevents the emission of USVs (Tukey test, $p < 0.05$). The results showed that LPS induced fever and anxiety-like behavior. Moreover, the HO-CO pathway is involved in the modulation of the emotional behavior in endotoxemic rats, since the treatment with an inhibitor of HO enzyme prevents the LPS effects.

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Poster

507. Stress, Anxiety, and Aversion

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Topic: G.03. Emotion

Support: NIMH MH 109545
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Title: Basolateral amygdala projections to the insular cortex mediate social approach to stressed rats

Authors: *A. DJERDJAJ, N. S. RIEGER, J. P. CHRISTIANSON;
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Abstract: Social vocalizations, chemosignals, and behavioral expressions of one's internal affective state shape the selection of social behavior responses made by others who detect these cues. A network of interconnected brain structures called the social decision making network (SDMN) integrates these stimuli and network output yields social behaviors that are appropriate for a given interaction. Deficits in SDMN connectivity underlie several psychiatric disorders such as schizophrenia and autism so further understanding the function of the SDMN may grant us new insight into aberrant social behaviors. The basolateral amygdala (BLA) and the insular cortex (IC) are reciprocally connected and each contribute to social and emotional behaviors. We explored the involvement of BLA projections to the IC in a social affective preference (SAP) test in which a test rat is presented with 2 juvenile conspecifics (PN30), 1 naïve to treatment and 1 stressed via 2 footshocks. Test rats prefer interaction with the stressed juvenile in this paradigm. Chemogenetic inactivation of the BLA via bilateral transduction of AAV-hSyn-hM4D(Gi)-mCherry followed by systemic administration of clozapine-N-oxide (3mg/kg) prior to SAP tests prevented test rat preference for the stressed juvenile. Further, inhibition of IC-projecting BLA neurons via CNO injection directly into the IC also prevented preference for the stressed juvenile. Ongoing investigations include retrograde tracing and Fos immunoreactivity and in vivo Ca2+ imaging of BLA-IC neuron activity during encounters with stressed conspecifics to elucidate the pattern of neuronal activity of BLA projections in the IC. The current results identify a new tract by which social emotional information is processed within the SDMN.

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Poster

507. Stress, Anxiety, and Aversion

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Korea Institute of Oriental Medicine (KIOM) (K18181)

Title: A spino-hypothalamo-habenular pathway mediating aversive behaviors

Authors: *S. LEE, Y. FAN, M. KIM, C. YANG, H. KIM;
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Abstract: Lateral habenula (LHb), an epithalamic region, is sensitive to aversive stimuli and controls aversive responses through projecting its output to ventral tegmental area which in turn reduces the dopamine release. Lateral hypothalamus (LH), the lateral region of hypothalamus, is also known to regulate aversive responses. Although the LHb has been shown to receive nociceptive inputs, it is not known yet how the somatosensory inputs enter the LHb, which receives input from structures. Thus, the present study attempted to elucidate whether the nociceptive inputs are delivered to the LHb via LH and thus leads to aversive behaviors. To prove it, we utilized extracellular recording, fast-scan cyclic voltammetry, and miniaturized fluorescence microscopy in Sprague-Dawley rats. In *in vivo* extracellular recording, nociceptive stimuli of tail pinch excited most LHb neurons (n=51), which was inhibited by chemical lesion of ibotenic acid in the LH, indicating mediation of LH. When responses of LH neurons (n=68) to tail pinch were recorded, 38 of the recorded neurons (38/68=55%) showed increases in firing rates. It was further confirmed by using the head-mounted miniaturized fluorescence microscopy. In the rats given GCaMP calcium indicators into LH, miniaturized fluorescence microscopy showed spontaneous increase of neuronal activity in response to tail pinch. In the fast-scan cyclic voltammetry, sustained decrease of dopamine efflux in the nucleus accumbens was found in the normal rats after pinching tail for 20 sec, which was abolished in the rats with a

chemical lesion of ibotenic acid in the LH. Our findings suggest that nociceptive inputs enter LHb via spino-hypothalamic pathway in order to generate aversive behaviors.

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Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

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Topic: G.03. Emotion

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Mong Junior Fellowship, Cornell Neurotech

Title: Ventromedial prefrontal parvalbumin neurons signal active avoidance

Authors: *Y.-Y. HO[1], Q. YANG[2], P. BODDU[3], M. R. WARDEN[1,4];
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Abstract: The medial prefrontal cortex (mPFC) plays an essential role in the suppression of passive behaviors and the facilitation of active behaviors in high-threat environments. mPFC parvalbumin (PV) neurons, which innervate the axon initial segment, cell body, and proximal dendrites of pyramidal neurons, gate mPFC signaling and play an important role in reward and fear extinction, working memory, and the allocation of attention. Here, we investigate the role of ventral mPFC (vmPFC) PV neurons in actions to avoid punishment and to obtain reward in freely moving mice. Animals were placed in an operant chamber and trained to cross to the opposite side of the chamber following an auditory cue. In the avoidance task, crossing the chamber within 5 seconds allowed the mouse to avoid receiving a shock. If the mouse failed to cross, the shock was turned on until escape occurred. In the approach task the mouse was required to cross the chamber within 5 seconds to obtain a water reward, and failure led to an aborted trial. We used fiber photometry to monitor the real-time population calcium dynamics of genetically defined vmPFC PV neurons in freely behaving mice. We injected AAV1-CAG-Flex-GCaMP6f into the vmPFC of PV-cre mice to express a genetically-encoded calcium indicator, and implanted an optical fiber over the vmPFC to monitor calcium-dependent fluorescence.

vmPFC PV neurons were strongly activated immediately prior to and during chamber crossing in successful avoidance trials, but were slightly suppressed during chamber crossing in successful approach trials. In addition, vmPFC PV neurons were active during chamber-crossing movements during the inter-trial interval during avoidance sessions, a response that only emerged after animals had experienced shock. No response to locomotion in the open field or during approach behavior was detected, and neural activity was not correlated with speed of movement. Since the auditory tone was turned off the moment the mouse successfully crossed the chamber, we also recorded neural activity during a modified version of the task, in which short auditory cues were used in some trials and auditory cues persisting beyond chamber crossing were used in others. We found that PV neural responses during shock avoidance were better explained by chamber crossing than by tone termination. Our results reveal that vmPFC PV neurons respond during actions to avoid threats.

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Poster

507. Stress, Anxiety, and Aversion

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Topic: G.03. Emotion

Support: McDonnell Fund for System Neuroscience
5T32AM108539-05

Title: Norepinephrine inhibits sensory neuron TRPV1 signaling in a sex- and stress-dependent manner

Authors: *L. V. THANG[1], M. K. MADASU[2], S. SINGH[3], J. GARCIA[4], R. AL-HASANI[6], J. G. MCCALL[5];
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Abstract: Exposure to stressful stimuli can suppress or enhance pain, a phenomenon known as stress-induced analgesia or hyperalgesia, respectively. The precise mechanisms of how stress affects pain is unclear. Similar to chronic pain, stress-related psychiatric disorders such as depression and anxiety are highly prevalent with poorly understood pathophysiology. Interestingly, females have twice the lifetime risk for depression and anxiety disorders and have greater pain prevalence when compared to her male counterparts. The exact neurophysiological underpinning for these sex differences is unknown. Chronic pain and stress lead to adaptations

that share significant overlapping physiology such that tricyclic and serotonin/norepinephrine reuptake inhibitor antidepressants are effective in treating chronic pain. Therefore, norepinephrine (NE) is likely one of the key neurotransmitters regulating pain processing during stress. Recent studies showed that activation of alpha 2-adrenergic receptors in the dorsal root ganglion (DRG) inhibits the transient receptor potential cation channel subfamily V member 1 (TRPV1), a polymodal molecular integrator in the pain pathway expressed in Aδ and C fiber nociceptors. However, it is unclear whether NE modulation of TRPV1 signaling is altered during chronic stress and whether this is sex-dependent. In this study, we show that social isolation stress, by singly-housing mice, increases paw-withdrawal thresholds to mechanical and thermal stimuli in both male and female mice. Using calcium imaging, we show that NE inhibits TRPV1 activation in the DRG of male group-housed mice, but not in female group-housed, or singly-housed mice of either sex. Furthermore, TRPV1-mediated calcium mobilization is higher in group-housed male mice compared to singly-housed male mice. This reduction in TRPV1-depdent calcium signaling may help explain the mechanism for social isolation stress-induced antinociception in male mice, but suggests this mechanism is NE-independent in female mice. Better understanding of stress-induced analgesia and its sex differences could aid in uncovering new, more targeted therapeutic targets for the treatment of pain and stress-related disorders.

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Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

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Program #/Poster #: 507.15/X10

Topic: G.03. Emotion

Title: Midbrain glutamatergic neurons drive locus coeruleus-mediated negative affect

Authors: *K. E. PARKER[1,3], A. R. BUCKLEY[1,3,4], S. L. STEWART[1,3], S. C. HUNTER[2,3,5], J. G. MCCALL[1,3];
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Abstract: More than 40,000 Americans commit suicide each year. Many of these victims suffered from stress-induced Major Depressive Disorder (MDD) and anxiety disorders. Many individuals of this susceptible population are particularly at risk, as current monoamine treatments for depression do not alleviate symptoms in a third of MDD patients. Further, many MDD patients have increased expression of N-methyl-D-aspartate (NMDA) glutamate receptors

in the locus coeruleus (LC), the main source of norepinephrine (NE) for the mammalian forebrain. Importantly, the LC is known to modulate stress-induced anxiety and resilience to chronic stress and is certainly positioned be an important modulator of stress-induced MDD. While glutamatergic modulation of LC-NE neurons is often associated with behavioral flexibility and attention, data from suicide victims points to an important role of glutamate signaling in the LC-NE system in modulating affective disorders and opiate withdrawal. Since previous studies have shown that blocking NMDA receptors has rapid antidepressant-like effects in humans and animal models, we investigated the neurocircuitry of traditional monoamine pathways and the role glutamate has in coordinating depressive-like phenotypes in mice. Specifically, we hypothesized that excitatory projections to the LC may modulate behaviors related to stress, depression, and anxiety. Using retrograde tracing techniques, we unveiled a prominent glutamatergic LC afferent projection and examined this newly identified projection using slice electrophysiology, *in vivo* optogenetics, and fiber photometry. Implementing behavioral assays including real-time place testing, elevated plus maze, and the open field test, we determined that this pathway plays a prominent role in mediating the LC's coordination of negative affective behaviors.

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Poster

507. Stress, Anxiety, and Aversion

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Program #/Poster #: 507.16/X11

Topic: G.03. Emotion

Support: CIHR Grant MOP89758

Title: Chemogenetic inhibition of neurons in the paraventricular nucleus of the thalamus that project to the nucleus accumbens has an anxiolytic effect on stress-induced anxiety

Authors: *X. DONG, S. LI, G. J. KIROUAC;
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Abstract: The paraventricular nucleus of the thalamus (PVT) is a member of the midline and intralaminar thalamic nuclei. Following a detailed analysis of fiber projections made by PVT neurons to its output targets, we found that most PVT neurons innervate the shell of the nucleus accumbens (NAcSh) and that these same neurons send collaterals to a wide range of cortical and subcortical targets associated with negative emotion and motivation, including prelimbic, infralimbic, and insular cortices, bed nucleus of the stria terminalis, the central nucleus of the amygdala. The pattern of the output distribution suggests a role of the PVT in the regulation of

aversion and stress-induced behavioral responses. This view is supported by experimental evidence that shows that the PVT mediates footshock induced anxiety-like behaviors and conditioned fear expression. In addition, projection-specific studies focusing on the PVT to NAcSh pathway have shown that this projection may be involved not only in food and drug seeking, but also in avoidance associated with morphine withdrawal and anxiety-like behaviors. The present study explored the role of the PVT to NAcSh pathway in stress-induced anxiety. We expressed Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the form of the inhibitory hM4Di in PVT neurons that project to the NAcSh using an intersectional dual-virus approach. One week after surgery, rats were exposed to an episode of moderately intense footshock (1.5 mA × 2 s × 5) and assigned to either high-responder group (HR) or low-responder group (LR) according to their level of fear (freezing time) in a novel context at 24 h after footshock. Stress-induced anxiety was measured at approximately 2 weeks post-footshock after a treatment of the hM4Di agonist clozapine (0.01mg/kg, i.p.) or saline. HRs showed a higher level of anxiety in a social approach and avoidance test compared to non-shocked animals and LRs. The elevated anxiety level was attenuated in clozapine treated HRs. There was no difference in anxiety levels between LRs and non-shocked rats. Clozapine had no effect on anxiety in LRs and non-shocked rats. Both HRs and LRs showed high level of freezing behavior when they were re-exposed to the shock context and clozapine treatment did not affect the expression of conditioned fear. The result suggests that the PVT to NAcSh pathway is involved in stress-induced anxiety-like behavior but not contextual fear. This study provides evidence for a role of a projection from the PVT to the NAcSh in stress-induced anxiety independent of contextual fear mechanisms.

Disclosures: **X. Dong:** None. **S. Li:** None. **G.J. Kirouac:** None.

Poster

507. Stress, Anxiety, and Aversion

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Topic: G.03. Emotion

Support: CIHR Grant MOP89758

Title: Extensive divergence of projections from neurons in the paraventricular nucleus of the thalamus to widespread regions of the forebrain

Authors: *S. LI, X. DONG, G. J. KIROUAC;
Rady Fac. of Hlth. Sci., Univ. of Manitoba, Winnipeg, MB, Canada

Abstract: The paraventricular nucleus of the thalamus (PVT) is an important component of the forebrain circuits involved in the mediation of appetitive and aversive behaviors. While the PVT

projects to a number of cortical and subcortical regions, work from our research group has established that the PVT projects most heavily to the shell of the nucleus accumbens (NAcSh), dorsolateral bed nucleus of the stria terminalis (BSTDL) and the lateral and capsular subnuclei of the central nucleus of the amygdala (CeL). Recent experimental evidence suggests that the PVT mediates distinctive behavioral responses in a projection specific manner. For example, a PVT projection to the CeL appears to be involved in conditioned fear whereas a projection to the NAcSh may be involved not only in avoidance associated with morphine withdrawal but also the regulation of food seeking. We have also shown with injections of the retrograde tracer cholera toxin B in a combination of NAcSh, BSTDL and CeL in the same animal that many neurons in the PVT provide collateral projections to NAcSh, BSTDL and CeL. However, the extent of these collateral projections is difficult to accurately determine using retrograde tracing alone. The present study used adeno-associated viruses (AAVs) to further evaluate the amount of fiber collateralization throughout the brain produced by PVT neurons. An AAV that transports in the retrograde direction to express the Cre-recombinase enzyme was injected in one of the target areas innervated by the PVT. Another AAV that is transported in the anterograde direction and transduces GFP in a Cre-dependent manner was injected in the PVT of the same animal. This resulted in GFP labeling of all collateral fibers made by PVT neurons associated with a specific projection. The density of fibers was quantified across all the cortical and subcortical projection targets associated with these injections. The global pattern of innervation to various forebrain regions made by different projection specific PVT neurons (NAcSh, BSTDL or CeL) was essentially the same with the NAcSh, BSTDL, and CeL receiving dense projections from these neurons while cortical and hypothalamic regions receiving less dense innervation. It is also clear that PVT neurons that primarily innervate the CeL or BSTDL send equally dense projection to the NAcSh. These results indicate that most PVT neurons innervate the NAcSh and send collaterals to a wide range of cortical and subcortical targets. How coordinated activity between the PVT and all of its cortical and subcortical targets regulates behavioral responses is unknown and will require innovative experimental approaches to resolve.

Disclosures: **S. Li:** None. **X. Dong:** None. **G.J. Kirouac:** None.

Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.18/X13

Topic: G.03. Emotion

Support: NIH Grant UH3-NS100548-01

Title: Treating psychiatric illness through targeted network disruption and electrical biomarker identification

Authors: M. BILGE[1], A. KANABAR[1], I. BASU[1], ***S. T. OLSEN**[3], M. J. BOGGESS[1], A. ROCKHILL[1], A. K. GOSAI[1], E. HAHN[1], C. CUSIN[1], T. DECKERSBACH[1], Z. WILLIAMS[2], D. D. DOUGHERTY[1], A. S. WIDGE[3];
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Abstract: Psychiatric disorders are increasingly understood as dysfunctions of hyper- or hypo-connectivity in distributed brain circuits. A prototypical example is Obsessive-Compulsive Disorder (OCD), which has been repeatedly linked to hyper-connectivity of Cortico-Striatal-Thalamo-Cortical (CSTC) loops. Deep brain stimulation (DBS) and lesions of CSTC structures have shown promise for treating both OCD and related disorders involving over-expression of automatic/habitual behaviors. Physiologically, we propose that this CSTC hyper-connectivity may be reflected in high synchrony of neural firing between loop structures, which could be measured as coherent oscillations in the local field potential (LFP). We have designed an Early Feasibility study in which we use the Medtronic PC+S device to simultaneously record and stimulate in the supplementary motor area (SMA) and Ventral Capsule/Ventral Striatum (VC/VS). Simultaneous recording of both structures lets us test the CSTC coherence hypothesis, while frequency-mismatched stimulation should disrupt that coherence and reduce compulsive symptoms. We report results from the first enrolled patient. Intraoperatively, we observed strong peaks in SMA-VCVS coherence in the theta (5-8 Hz) and alpha (8-15 Hz) bands, consistent with the initial hypothesis. We were further able to monitor SMA-VCVS coherence for over a year, with daily recordings that fluctuated as the patient's clinical status changed. Combined SMA-VCVS stimulation dramatically decreased subjective experience of mood and OCD symptoms, with an approximately 5-point drop in clinical rating scales. Further, there was a marked disruption of SMA-VCVS coherence across the theta and alpha bands, specifically with loop-disrupting stimulation and not with DBS alone. Theta coherence correlated with improvement in symptoms, although we observed stronger effects in the gamma (30-55 Hz) band. We will discuss implications of these results for network modulation more broadly, across the psychiatric disorders.

Disclosures: M. Bilge: None. **A. Kanabar:** None. **I. Basu:** None. **S.T. Olsen:** None. **M.J. Boggess:** None. **A. Rockhill:** None. **A.K. Gosai:** None. **E. Hahn:** None. **C. Cusin:** None. **T. Deckersbach:** None. **Z. Williams:** None. **D.D. Dougherty:** None. **A.S. Widge:** None.

Poster

507. Stress, Anxiety, and Aversion

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 507.19/X14

Topic: G.03. Emotion

Support: NIH Grant 1R21MH109722-01A1
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MGH-MIT Grand and Challenges program
The Brain & Behavior Research Foundation
The Harvard Brain Initiative Bipolar Disorder Fund supported by Kent & Liz Dauten

Title: Alteration of brain connectivity and behavior using a precisely timed electrical stimulation paradigm in a fear regulation circuit

Authors: *M.-C. LO, R. L. YOUNK, E. B. BLACKWOOD, A. E. REIMER, A. S. WIDGE; Psychiatry, Univ. of Minnesota, Minneapolis, MN

Abstract: Information flow in brain networks may depend on the oscillatory synchrony of local field potential (LFP) between regions. For fear-related disorders, the connection between the medial prefrontal cortex (mPFC) and basolateral amygdala (BLA) is particularly important. Theta-band (4-8 Hz) PFC-BLA LFP synchrony correlates with the ability to learn and recall safety memories. Clinical exploitation of this knowledge is limited by the lack of established paradigms to alter inter-area synchrony. This work aims to alter PFC-BLA connectives and assess behavioral outcomes in rodents.

Electrodes with 8 recording channels and one stimulating channel were implanted into infralimbic cortex (IL, the rodent homologue of mPFC) and BLA of Long-Evans rats. Rats underwent fear conditioning and extinction, with bar press suppression and freezing as behavioral measures. On the Extinction day, rats received either SHAM (connected without stimulation, N=10) or paired electrical stimulation (N=10), which delivered pulse trains (100 μA and 90 μs pulse width, 6Hz) simultaneously into IL and BLA with 180^{o} phase lags (IL leading), prior to the extinction session. Electrophysiological signals were recorded throughout the entire behavioral experiment. We measured entrainment of the low-frequency LFP (coherence) and synaptic connectivity changes against baseline. For the ERP measurements, 50 single biphasic pulses (100 uA and 90 μs pulse width) were delivered to either IL or BLA and LFPs from the other region were recorded.

Rats that received paired, theta-frequency electrical stimulation exhibit more effective fear regulation compared to the SHAM group with 1) faster fear extinction rate on the Extinction day (decrease in freezing and bar press suppression) and 2) less fear response on the Recall day. We also expect the paired electrical stimulation to enhance both the coherence in the theta band (4-8 Hz) and top-down synaptic connectivity in the IL-to-BLA direction, both post-stimulation and during extinction and recall sessions.

In summary, we have proposed a paired electrical stimulation technique to alter brain oscillatory synchrony and behavior. This may provide a new technique for neuroscientists to study brain networks. It may provide causal evidence for oscillatory synchrony as a key communicative mechanism. The intervention may eventually lead to more effective therapies for treatment-resistant varieties of psychiatric disorders.

Disclosures: M. Lo: None. **R.L. Younk:** None. **E.B. Blackwood:** None. **A.E. Reimer:** None. **A.S. Widge:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.01/X15

Topic: F.04. Stress and the Brain

Support: NIH Grant R15MH104836
NIH Grant R15MH116337

Title: Impact of immediate, pre-learning stress on the acquisition, extinction, and generalization of fear in a fear-potentiated startle paradigm

Authors: *P. R. ZOLADZ[1], M. R. RIGGENBACH[1], J. N. WEISER[1], B. E. MOSLEY[1], J. J. HIPSKIND[1], L. E. WIREMAN[1], K. L. HESS[1], T. J. DUFFY[1], J. K. HANDEL[1], M. G. KASCHALK[1], K. E. RENEAU[1], S. J. HELWIG[1], B. R. RORABAUGH[2], S. D. NORRHOLM[3], T. JOVANOVIC[3];
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Abstract: Stress time-dependently affects hippocampus-dependent learning and memory. Stress administered immediately before learning enhances long-term hippocampus-dependent memory, while stress that is temporally separated from learning impairs long-term hippocampus-dependent memory. Limited work has addressed the time-dependent effects of stress on learning that is dependent on other brain areas, such as the amygdala. Therefore, in a set of two experiments, we extended previous work examining the time-dependent effects of stress on learning by assessing the impact of immediate, pre-learning stress on fear conditioning and fear generalization. In both experiments, healthy participants underwent a stress (socially evaluated cold pressor test) or control manipulation immediately before completing differential fear conditioning in a fear-potentiated startle paradigm. In Experiment 1, participants completed extinction and extinction memory sessions 24 and 48 h after conditioning, respectively. In Experiment 2, participants completed generalization testing 24 h after conditioning. Results from Experiment 1 revealed that stress administered immediately before acquisition enhanced baseline startle and fear learning, evidenced by greater fear-potentiated startle to the CS+. Although no group differences were observed during extinction training, stressed participants exhibited evidence of impaired extinction memory 48 h after training. Importantly, stressed participants' cortisol responses to the stressor on Day 1 were positively associated with CS discrimination during extinction and extinction memory testing. Results from Experiment 2 are currently being assessed. Thus far, our findings suggest that stress immediately before fear conditioning results in a stronger, more enduring fear memory, perhaps via corticosteroid activity. Such a paradigm could be useful for understanding factors that influence traumatic memory formation.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.02/X16

Topic: F.04. Stress and the Brain

Title: Stress that is temporally separated from learning sex-dependently affects long-term memory in a forced confabulation paradigm

Authors: ***K. E. RENEAU**[1], M. R. RIGGENBACH[1], J. N. WEISER[1], L. E. WIREMAN[1], M. G. KASCHALK[1], S. J. HELWIG[1], B. R. RORABAUGH[2], K. E. PAYMENT[1], P. R. ZOLADZ[1]; [1]Psychology, Sociology, & Criminal Justice, [2]Pharmaceut. & Biomed. Sci., Ohio Northern Univ., Ada, OH

Abstract: Stress exerts time-dependent effects on learning and memory. Stress administered immediately before learning enhances long-term memory, while stress that is temporally separated from learning impairs long-term memory. Research examining the time-dependent effects of stress on false memory formation is limited. We previously reported that stress administered immediately before learning prevented false memory development in participants who exhibited a blunted cortisol response to the stressor. In the present study, we examined the impact of stress administered 30 min before learning on false memory development in a forced confabulation paradigm. We predicted that stress temporally separated from learning would impair the storage of a witnessed event and increase participants' susceptibility to false memory development. Eighty-six participants underwent a stress (socially evaluated cold pressor test) or control manipulation 30 min before viewing an 8-min excerpt from the Disney movie *Looking for Miracles*. The next day, participants were interviewed and asked questions about the video, some of which forced them to confabulate responses. Three days and three weeks later, respectively, participants completed a recognition test in the lab and a free recall test via email. Results revealed a robust misinformation effect, overall, as participants falsely recognized a significant amount of confabulated information as having occurred in the original video. Stress, overall, did not significantly influence this misinformation effect. However, participants' cortisol responses to the stressor were positively associated with the recall of confabulated information. Moreover, stress impaired the recognition of actual events that occurred in the video in males, while enhancing such recognition in females. These findings suggest that stress-induced increases in cortisol might result in greater recollection of misinformation. They also indicate

that stress temporally separated from learning selectively impairs memory accuracy in males and enhances memory accuracy in females, which is consistent with previous research from our laboratory.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.03/X17

Topic: F.04. Stress and the Brain

Title: Impact of stress and the timing of misleading questions on false memory formation

Authors: *M. R. RIGGENBACH[1], B. R. RORABAUGH[2], K. E. PAYMENT[1], P. R. ZOLADZ[1];
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Abstract: Stress can enhance, impair, or have no effect on learning and memory. One factor that determines the type of effect that stress exerts on learning and memory is the timing of the stress relative to learning. When stress is administered around the time of learning, long-term memory is generally enhanced; when stress is temporally separated from learning, long-term memory is generally impaired. Research examining the impact of stress on false memory formation has been conflicting. It is possible that the timing of stress relative to the acquisition of misinformation could influence false memory development. Thus, we examined the time-dependent influence of stress on the misinformation effect in a forced confabulation paradigm. Seventy-three participants (31 males, 42 females) submerged their hand in a cold (stress) or lukewarm (no stress) water bath and then watched a 9-min excerpt from *Return of the Pink Panther*. Ten or twenty-five minutes after the water bath manipulation, participants were asked questions about the video, some of which forced participants to confabulate answers. Salivary cortisol levels were assessed before and after the water bath in order to evaluate stress-induced alterations of cortisol levels. Twenty-four hours later, participants were given a memory test that asked them to determine which events actually occurred in the video and which did not. They were also asked to provide a confidence rating for each answer. Three weeks following the memory test, participants were contacted via email to complete a free recall test. Overall, participants exhibited a misinformation effect and recognized a significant amount of false information as having actually occurred in the original video. There was no significant effect of stress on false memory formation. However, participants who were interviewed 25 min after the

water bath manipulation recognized significantly more false information as having occurred in the original video than participants who were interviewed 10 min after the water bath manipulation. These findings suggest that interviewing individuals closer in time to a witnessed event decreases their susceptibility to identifying false information as having occurred in the witnessed event.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.04/X18

Topic: F.04. Stress and the Brain

Support: The BraveNet Coordinating Center at Einstein Seed Grant

Title: The effects of mindfulness-based interventions on sustained attention and inhibitory control

Authors: *E. M. MOHR[1], T. BRANDMEYER[3], R. HECHT[3], R. S. GUPTA[4], P. L. A. SCHOENBERG[1], D. R. VAGO[2];
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Abstract: Mindfulness-Based Interventions (MBIs) are a family of standardized cognitive and behavioral therapies that focus on cultivating mindfulness-related skills for improving maladaptive cognitive, emotional, and behavioral processes. MBIs have been developed for a wide range of problems, disorders, and populations and are increasingly available in a variety of health settings. Empirically supported MBIs include acceptance and commitment therapy (ACT), dialectical behavior therapy (DBT), mindfulness-based cognitive therapy (MBCT), and mindfulness-based stress reduction (MBSR). As the empirical evidence for the efficacy of these interventions continues to grow, the importance of investigating the mechanisms or processes by which they lead to beneficial outcomes is increasingly recognized. The purpose of the present study was to investigate the behavioral and cognitive mechanisms by which MBIs may improve health outcomes. Specifically, we sought to examine engagement between MBSR, perceived levels of stress, and performance on an emotional variant of a Go-NoGo task. Individuals with moderate to high levels of stress will be recruited (n=30). Perceived levels of stress, measured by the Perceived Stress Scale (PSS), and performance on an emotional Go-NoGo task will be assessed before and after MBSR. The Go-NoGo task included 600 negative, positive, and neutral

words. Although data is still being collected, preliminary post-MBSR testing showed a decrease in stress levels. Post-testing also showed performance changes in the Go-NoGo task. Preliminary data showed an increase in hit rates for negative, positive, and neutral words, and a decrease in false alarm rates for negative, positive, and neutral words. Results also showed a decrease in reaction times for negative and positive words, and an increase in reaction times for neutral words. These preliminary results suggest MBSR targets self-regulatory mechanisms, leading to changes in perceived stress.

Disclosures: **E.M. Mohr:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **T. Brandmeyer:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **R. Hecht:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **P.L.A. Schoenberg:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **R.S. Gupta:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine. **D.R. Vago:** A. Employment/Salary (full or part-time):; Osher Center for Integrative Medicine.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.05/X19

Topic: F.04. Stress and the Brain

Title: Can EEG explain obesity-related cognition during exercise?

Authors: *J. BENAVIDEZ[1], C. DY[1], H. TRAN[1], M. MIYAKOSHI[2], S. KESLACY[1]; [1]Sch. of Kinesiology & Nutritional Sci., California State University, Los Angeles, Los Angeles, CA; [2]Swartz Ctr. for Computat. Neuroscience, Inc, UCSD, La Jolla, CA

Abstract: Introduction: A developing body of evidence depicts that obesity may induce damaging effects to brain health, decreasing cognitive performance & increasing the risk of dementia. Exercise may be one of few prophylactic strategies against cognitive decline. However, it is still unknown if exercise has a beneficial effect on obesity-related cognition. Additionally, robust measurements of brain activity remain difficult but could give insight to possible mechanisms that are induced by obesity. This study aims to determine if exercise affects cognitive performance and brain activity in healthy-obese (HO) compared to healthy non-obese (HNO). We hypothesize that HO will have a difference cognitive performance during exercise compared to HNO. Methods: 15 healthy male adults, 10 (HNO BMI<30) & 5 (HB BMI>30) with average age 24 ± 3 y.o. have participated in this study. During a 1st visit, participants completed health-questionnaires, anthropometric measures, familiarization with Stroop task, and a VO2max (Cosmed Quark-CPET) to determine peak performance. On the 2nd visit, EEG was recorded during a resting condition (5-min eyes closed), baseline Stroop (Strp1), Stroop during

steady-state exercise (Strp2) at 50% of VO2max on a Lode Sport Excalibur (20 min.) & lastly a post exercise Stroop (Strp3). EEG was measured by Mobita TMSi, sampled at 250Hz using 10-20 international system recorded at 24 sites including 2 EOG artifact electrodes. Data was acquired on Biopac Acqknowledge Software 4.2 & offline analysis will be performed on EEGLAB12.1.2b. Stroop was performed using the Psychtoolbox-3 for 20 trials recording RT (sec) and errors (ER). Results: HNO have a greater VO2max vs HO (47.76 ± 3.84 ml.kg.min-1 vs 33.68 ± 3.05 ml.kg.min-1; $p<0.05$). Error were lower for NO vs HNO before exercise (7.6 vs 1.5ER; p=.01). Results of comparing HNNO showed a faster RT and less ER compared to s HNO during exercise (243.09s vs 323.91s; p=.031 & 4.3 vs 10.6; p=.001). After exercise, HO showed more errors than HNO (5.2 vs 3.0ER; p=.04). Conclusion: This study is the first to demonstrate differences in the effect of exercise on obesity and brain performance. EEG data will provide insight on possible mechanisms. Our preliminary data are promising in dissecting the role of exercise on obesity related brain function.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.06/X20

Topic: F.04. Stress and the Brain

Support: CDMRP Grant W81XWH-17-C-0088

Title: Disentangling the effects of subjective task load and task performance on neuroendocrine stress response

Authors: *K. LAFOLLETTE[1], B. C. SATTERFIELD[2], M. LAZAR[2], W. D. S. KILLGORE[2]; [1]Psychiatry & Behavioral Sci., Stanford Univ., Stanford, CA; [2]Psychiatry, Univ. of Arizona, Tucson, AZ

Abstract: Introduction: Subjective task load, the perceived demands for resources to engage in a task, are often conflated with stress response and actual task performance. While recent efforts have laid the groundwork for disentangling stress and performance from mental/cognitive load, few studies have considered other variants of task load, such as time and performance pressure. Here we investigated the effects of objective task performance and subjective task load on cortisol stress response. We hypothesized that task load would significantly predict stress response and that task performance relevant to the loading variant would partially mediate this relationship.
Methods: 120 adults (62 F; 21.6±3 yrs) completed three neurocognitive assessments as part of a

prolonged assessment battery (two-stage reinforcement learning, response inhibition, and tapping tasks) and psychosocial stressor. The NASA Task Load Index was administered following the neurocognitive assessment block to assess subjective task load. Saliva samples were collected twice upon arrival and once immediately after task administration to assess changes in cortisol stress response. Multiple regression models were used to predict stress reactivity using task loadings as predictors. Post-hoc mediation analyses included objective performance metrics that were determined to be associated with the loadings.
Results: Linear regressions demonstrated that mental, physical, and performance-based task load significantly predicted stress response ($F>4.1$, $p<0.05$). Subsequent models determined *mental load* significantly predicted model-free strategy and *performance load* predicted both money earned and model-free strategy on the two-stage task ($F>4.28$, $p<0.04$), while *physical load* was found to predict total number of taps and reaction time on the tapping task ($F>5.07$, $p<0.03$). Task loadings were not predictive of performance on the response inhibition task. Post-hoc causal mediation analyses determined that none of the direct effects of task load on stress reactivity were mediated by objective task performance ($abs(b)<0.15$, $p>0.84$).
Conclusions: These findings suggest that stress reactivity during performance can be predicted by a number of subjective task loading variants. Furthermore, the effect of these loads is not explained by standard metrics of objective task performance. Such findings emphasize the importance of subjective experience during task performance beyond the scope of task yields, with implications for a wide array of applications, such as the teaching of new skills or performance assessment.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.07/DP10/X21

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: F.04. Stress and the Brain

Support: FAPESP 2009/13911-6

Title: Environmental pollutants influence stress hormone and memory: Implications to brain health in human aging

Authors: *J. N. SOUZA-TALARICO[1], P. PLUSQUELLEC[3], S. J. LUPIEN[4], F. C. SILVA[2], D. SUCHECKI[5];
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Abstract: Background: Chlorinate pollutants still have wide industrial and commercial applications despite evidence regarding their negative effects on human. For decades the endocrine disruptive effect of the chlorinate pollutants has been demonstrated in the gonadal system. However, endocrine disruptors are capable of interfering on steroids hormones implying that chlorinate pollutants may act on cortisol concentration by disrupting the hypothalamic-pituitary-adrenal (HPA) axis and therefore impairing memory performance through impact on hippocampus, the main neuronal structure responsible for the HPA axis negative feedback. However, there is no evidence to support that. This is a relevant issue since HPA dysfunction is associated with vulnerability to several disorders including those related to brain and cognition. **Objective**: to analyze the influence of chlorinate pollutants on diurnal cortisol concentration and memory performance in older adults. **Methods**: Using a cross-sectional study design, polychlorinated biphenyls (PCB) and organochlorine (OC) pesticide concentrations, known chlorinate pollutants, were determined from blood samples of 128 cognitively healthy older adults (83.6% female; Age: M=65.8, SD±7.9; Years of education: M=9.7, SD±4.4). Salivary cortisol was collected at home over 2 days at awakening, 30 min. after waking, afternoon (~3PM) and evening (~10PM) periods. Declarative memory was assessed using the California Verbal Learning Test (CVLT). **Results**: Multivariate regression (MR) analysis, controlling for gender, age and education, revealed a significant PCB effect on diurnal cortisol concentration (β= -0.241, R^2 = 0.103; p = 0.002). Similarly, PCB (β= -0.205; p = 0.022) and OC compounds were negatively associated with low CVLT scores (β = -0.293; p = 0.001), explaining 9% of the memory performance variability in the MR model (R^2 = 0.09; p = 0.001). **Conclusion**: Environmental chlorinate pollutants may influence cortisol and memory during aging. Our findings may set the stage for longitudinal studies investigating whether cumulative exposure to chlorinate pollutants represent a risk factor for stress-related and cognitive disorders later at life and therefore to sustain public policy strategies to control environmental contaminant exposure aiming the brain health promotion during aging.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.08/X22

Topic: F.04. Stress and the Brain

Support: ERC-2015-CoG

Title: Predicting real-life stress reactivity from the effects of acute stress on brain function

Authors: *R. TOUTOUNJI[1], B. KAPTEIJNS[1], M. KRENTZ[1], F. KRAUSE[1], L. D. DE VOOGD[2,1], E. VASSENA[1], E. J. HERMANS[1];
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Abstract: Rationale
Acute stress affects the brain on multiple levels, including that of large-scale brain networks. Research has implicated the salience (SN), executive control (ECN), and default mode (DMN) networks in this process. These effects have also been shown to be time dependent, varying across the duration of the stress response, while also resulting in different behavioral changes across the time course. This evidence stems from multiple, cross-species studies, however, the full extent of the effects of stress on these networks in humans has not been investigated. Furthermore, individual stress reactivity can vary greatly from person to person. This inter-individual difference can be seen in reactivity to daily life stressors. Here, we investigate whether the temporal dynamics of the neural response to acute stress can predict stress reactivity in daily life.
Methods
One-hundred medical students will be recruited. Participants undergo two, counter balanced fMRI sessions: a stress session, with acute stress induction implemented with the socially evaluated cold pressor test (SECPT), and a control session. During scanning, 3 tasks are performed, known to elicit activity in the SN (oddball), DMN (associative memory), and ECN (2-back), intermixed with resting state blocks, and physiological monitoring. Participants also undergo experience sampling during an exam (i.e. stress) and a non-exam (i.e. control) weeks. Survey data and physiological measures will be acquired using smartphones and wristbands, allowing for the investigation of real-life stress during both weeks.
Results
Initial results (n=39) show a significant increase in self-reported stress measures during the stress week (event, activity, mood, and social stress; all $P<0.01$; but not physical stress), thus validating an exam week is more stressful than a non-exam week. Preliminary fMRI analyses (n=16) confirm that the employed tasks recruit the SN, DMN, and ECN networks, and confirm increased stress responses to the SECPT, shown by decreased heart rate variability. Further analyses will focus on linking subjective stress with physiological stress measures acquired in real life. Importantly, we will investigate how the effects of stress on brain function predict real-life stress reactivity.
Conclusions
Current results confirm the validity of our real-life stress reactivity measures, including variability in real-life stress reactivity, which is essential to examining inter-individual differences. Analysis of fMRI data show that the tasks are engaging the corresponding networks

This study will yield insight into the biological basis of stress sensitivity and reactivity in real life.

Disclosures: R. Toutounji: None. **B. Kapteijns:** None. **M. Krentz:** None. **F. Krause:** None. **L.D. De Voogd:** None. **E. Vassena:** None. **E.J. Hermans:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.09/X23

Topic: F.04. Stress and the Brain

Title: Relationship between academic stress and heart rate variability (HRV) patterns for college athletes

Authors: *N. RAJ[1], M. DITOMMASO[1], A. JOHNSON[2], R. E. JOHNSON[1];
[1]Mechanical Engin. and Bioengineering, [2]Data Sci., Valparaiso Univ., Valparaiso, IN

Abstract: Stress is common in college students, and can cause low academic performance, depression, and anxiety. Student athletes typically experience higher stress levels due to rigorous training, travel schedules, and competition [1]. Some level of stress is healthy: performance peaks at an optimum level of stress called eustress. But as stress increases, performance and health decline and burnout can occur [2]. One strategy for monitoring physiological stress is to measure heart rate variability (HRV). HRV is often used in athletics to monitor training load and recovery; however, for many student athletes, the effects of academic stress may confound these results and is less well studied. To properly interpret HRV patterns and optimize training, we need to better understand the physiological effects of academic stress on student athletes.
In this experiment we studied the relationship between perceived stress and HRV in college athletes. Perceived stress was measured using a daily survey where athletes indicated their stress on a scale from 1 (very stressed) to 5 (not stressed). HRV was measured using a chest belt heart rate monitor from Firstbeat Technology, with which athletes recorded five minutes of data soon after waking up each morning. This data was used to calculate a Recovery Index (ranging from 0 to 100%), which estimates how fully athletes have recovered from training and how well the autonomic nervous system is functioning [3]. 27 players on an NCAA Division I women's soccer team participated in this study, which was approved by the Valparaiso University IRB. Data was collected from Aug. to Oct. in 2017.
We found that perceived stress significantly affected the HRV-based Recovery Index. When athletes rated their stress as a 2, the median Recovery Index was 47.3%. When athletes rated their stress as a 3, the median Recovery Index was 55.3%. Stress levels 4 and 5 had a median Recovery Index of 57.3% and 57.8%, respectively. In summary, higher perceived stress was linked to lower HRV and decreased recovery. These results suggest that academic stress can

have a significant effect on the physiological recovery of college athletes.
[1] 2018 Chyi et al., PeerJ.
[2] 2015 Bali, Int J Phys Ed, Sports, & Health.
[3] 2017 Nuuttila et al., Int J Sports Med.

Disclosures: **N. Raj:** None. **M. DiTommaso:** None. **A. Johnson:** None. **R.E. Johnson:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.10/X24

Topic: F.04. Stress and the Brain

Support: CSC NO. 201606750009

Title: Interactive effects of childhood stress and acute stress on prefrontal resting-state connectivity

Authors: *H. WANG[1], L. D. DE VOOGD[2], R.-J. VERKES[1], B. ROOZENDAAL[1], G. FERNANDEZ[1], E. J. HERMANS[1];
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Abstract: Dynamic adaptation to stress is essential for coping with daily life challenges and chronic stress. Stress reactivity is regulated in the central nervous system through coordinated activity in limbic and prefrontal brain regions, such as the amygdala, hippocampus, and ventromedial prefrontal cortex (vmPFC). Previous studies have shown changes in functional connectivity (FC) between these regions both after exposure to childhood stress and during acute stress, but it remains unknown whether these two factors interact. In current study, we therefore investigated the interactive effects of childhood stress and acute stress on prefrontal FC during rest. We furthermore explored if such interactions could be mediated by altered HPA-axis function. 120 healthy volunteers underwent resting-state functional MRI (7 min) after a standardized stress induction and control procedure. All participants completed the childhood trauma questionnaire (CTQ), and saliva samples were collected five times to assess HPA-axis function. BOLD-fMRI voxel time courses were extracted and averaged for bilateral amygdala, hippocampus and ventromedial prefrontal cortex (vmPFC). FC was calculated using (Fisher's z transformed) pairwise Pearson's correlations after correction for motion and physiological nuisance variables. FC data were analyzed using repeated-measures ANOVAs with stress as within-subject factor, and non-parametric correlations (for differential FC, CTQ scores and salivary hormone levels) was carried out. The results showed acute stress decreased hippocampus-vmPFC resting-state FC compared to the neutral control session. This decrease

was qualified by an interaction with CTQ score, indicating that the reduction of FC in these circuits was exacerbated in individuals with higher CTQ scores. CTQ scores were furthermore negatively associated with basal cortisol levels. However, we found no evidence that basal cortisol (partially) mediated the interaction between CTQ scores and differential FC between these regions. Our findings show that exposure to stressful life events during childhood alters the neural response to acute stress in neural circuits known to be involved in stress adaptation and emotion regulation in a sample of healthy volunteers recruited from a student population. In line with earlier studies in several patient populations, childhood adversity was also associated with blunted basal HPA-axis function. Although we found no statistical evidence of mediation in this relatively healthy sample, future research should address the question whether blunted HPA-axis during development plays role in altering central response to stressors.

Disclosures: H. Wang: None. **L.D. de Voogd:** None. **R. Verkes:** None. **B. Roozendaal:** None. **G. Fernandez:** None. **E.J. Hermans:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.11/X25

Topic: F.04. Stress and the Brain

Title: Evaluation of stress-reducing interventions in an undergraduate student population: Perceived stress, blood pressure, frontal EEG asymmetry, and salivary immunoglobulin-alpha

Authors: L. ANDERSEN[1], S. GOWAN[2], B. RONNESTRAND[1], B. TAYLOR[3], *M. WONG[1]; [1]Psychology, [2]Biol., [3]Microbiology, Univ. of Wisconsin-La Crosse, La Crosse, WI

Abstract: High levels of stress are reported by undergraduate students globally, but how do we combat student stress? Mindfulness meditation is commonly used to reduce stress. Here we aim to investigate the relative effectiveness of different forms of stress-reducing interventions compared to mindfulness meditation. In our first study, all participants were undergraduate students at the University of Wisconsin-La Crosse. Participants in our first study either completed a mindfulness meditation exercise (n = 30) or played Flower (n = 29), a simple instruction-free video game, for 20 minutes. There is some suggestion from the literature that an instruction-free game that requires little training may be effective for stress reduction. Before and after each intervention, we recorded participant self-perceived stress (using an abbreviated, modified version of the Psychological Stress Measure-9) and measured participant heart rate and blood pressure. Preliminary data analyses revealed a statistically significant (pre to post) reduction across all measures of stress ($p < 0.05$), but no statistically significant difference between playing Flower and meditating. We next wondered how another type of stress intervention, listening to a stress management audiobook, compares to mindfulness meditation in

reducing student stress. In this second, ongoing study, we wish also to investigate what effects, if any, these two forms of stress interventions have on the nervous and immune systems. To assess the effect stress has on the nervous system, we are using electroencephalography to examine the relative left versus right frontal lobe alpha-wave asymmetry. Greater left than right alpha-wave asymmetry is indicative of a more relaxed state of mind. To assess the effect stress has on the immune system, we are using an enzyme-linked immunosorbent assay to quantify the level of the antibody immunoglobulin-alpha (IgA) present in participants' saliva. Higher levels of IgA are indicative of a stronger immune system. Given the results of the first study, we hope the second follow up study will elucidate the neurophysiological and immunological effects of stress-reducing interventions on undergraduate students.

Disclosures: L. Andersen: None. **S. Gowan:** None. **B. Ronnestrand:** None. **B. Taylor:** None. **M. Wong:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.12/X26

Topic: F.04. Stress and the Brain

Title: Silver brain: Forget bingo, start virtual cardio

Authors: *H. TRAN[1], T. ESGUERRA[1], E. PUENTE[1], A. MUNOZ[1], V. GONZALEZ[1], S. KESLACY[2];
[1]California State Univ. of Los Angeles, Los Angeles, CA; [2]Kinesiology, CSULA, Los Angeles, CA

Abstract: Aging is the most important risk factor for cognitive decline, partly due to the attenuation of brain oxygenation. Exercise enhances muscle oxygenation but has not being shown to increase brain oxygenation. The emergence of Virtual Reality (VR) technology could prove to be meaningful and relevant to stimulate the brain. There is a lack of studies on the effect of VR and exercise on cerebral and muscle oxygenation across ages. **Purpose:** to assess the effect of VR on exercise-induced change in cerebral oxygenation in elderly.We hypothesized that there would be a greater augmentation of cerebral oxygenation ($CerO_2$) in the prefrontal cortex (PFC) while cycling with VR compared to the No-VR condition for the elderly. **Methods:** Both young male and female participants (n=4, 23±2 years) and old male and female participants (n=4, 55±25 years) first performed a graded VO_{2max}test on a cycle ergometer (828E, Monark) and returned to the lab to perform the VR paradigm. The VR test was performed on a stationary bicycle made to synchronize with a cycling game (VR bike, ViRzoom). Participants wore a virtual reality headset (Playstation 4, Sony) and cycled at a moderate intensity (60% of Pmax). Near-infrared spectroscopy (NIRS, Artinis Oxymon MkIII) was used to measure O_2Hb,

deoxyhemoglobin (HHb), and total hemoglobin (tHb) from the left and right frontal brain cortices (LFC, RFC) and the right vastus lateralis (RVL) muscle.**Results:** BrainO_2Hb mean values increased with exercise. The right frontal cortex O_2Hb increased with VR, but there was no difference for the left frontal cortex (RFC 6.1 vs 10.4; LFC 9.3 vs 9.4 fold). Muscle O_2Hb decreased (13.1 vs 11.6 fold) with VR. Brain HHb increased with VR in the LFC (RFC -10.6 vs 11.5 and LFC -4.8 vs 1.0) while muscle HHb decreased (-1.3 vs. 27.6 fold). There was a trend for tHB to decrease for both muscle and brain during exercise with VR.We will compare young adults and elderly.**Conclusion**: Our preliminary data are promising, and we hope to provide an alternative approach to increase cerebral stimulation and to contribute additional understanding on the cerebral and muscle hemodynamics of exercise in VR milieu and affect cognitive decline in the aging population.

Disclosures: H. Tran: None. **T. Esguerra:** None. **E. Puente:** None. **S. Keslacy:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.13/X27

Topic: F.04. Stress and the Brain

Support: Air Force Research Laboratory FA-8650-15-2-5518

Title: Biomarkers of stress reactivity in animals and humans

Authors: *S. T. JENZ[1], J. MECKES[1], P. H. LIM[1], S. GOLDSTEIN[1], S. L. WERT[1], E. TUNC OZCAN[1], R. JANKORD[2], R. SHIA[2], E. E. REDEI[1];
[1]Psychiatry and Behavioral Sci., Northwestern Univ. Feinberg Sch. of Med., Chicago, IL; [2]Air Force Res. Lab., Wright-Patterson Air Force Base, OH

Abstract: Most people have experienced a stressful period of time during their life, however the way each person reacts to stress is unique for each individual. Some can recover from a stressful period fast without any physical or mental consequences, while others find it difficult to get back to high level functioning or take longer to do so. This study aims to identify biomarkers that can be used to quantity stress-reactivity between resilience, the ability to overcome stress, and vulnerability, the failure to overcome stress, for an individual. In an animal study, candidate blood RNA markers for stress responsiveness were identified from rat less stress-reactive and more stress-reactive rat strains using their memory changes after prolonged stress as indicators of their cognitive stress-reactivity. By aligning these memory changes with transcriptional consequences of stress in these strains, biomarkers that showed parallel significant changes between blood and the hippocampus were selected. The present study applies these findings to human subjects. Serum samples from Air Force trainees were obtained before, during, and after

intensive physical and mental training. This training represents repeated, prolonged stress to the trainees. Serum protein concentration of the candidate blood markers of stress were quantified across the training. Results show that individual variations in response to stress are large and that each subject's individual trends in biomarkers compared to other biological markers measured throughout the period of training can be associated with their overall evaluation in the training.

Disclosures: S.T. Jenz: None. **J. Meckes:** None. **P.H. Lim:** None. **S. Goldstein:** None. **S.L. Wert:** None. **E. Tunc Ozcan:** None. **R. Jankord:** None. **R. Shia:** None. **E.E. Redei:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.14/X28

Topic: F.04. Stress and the Brain

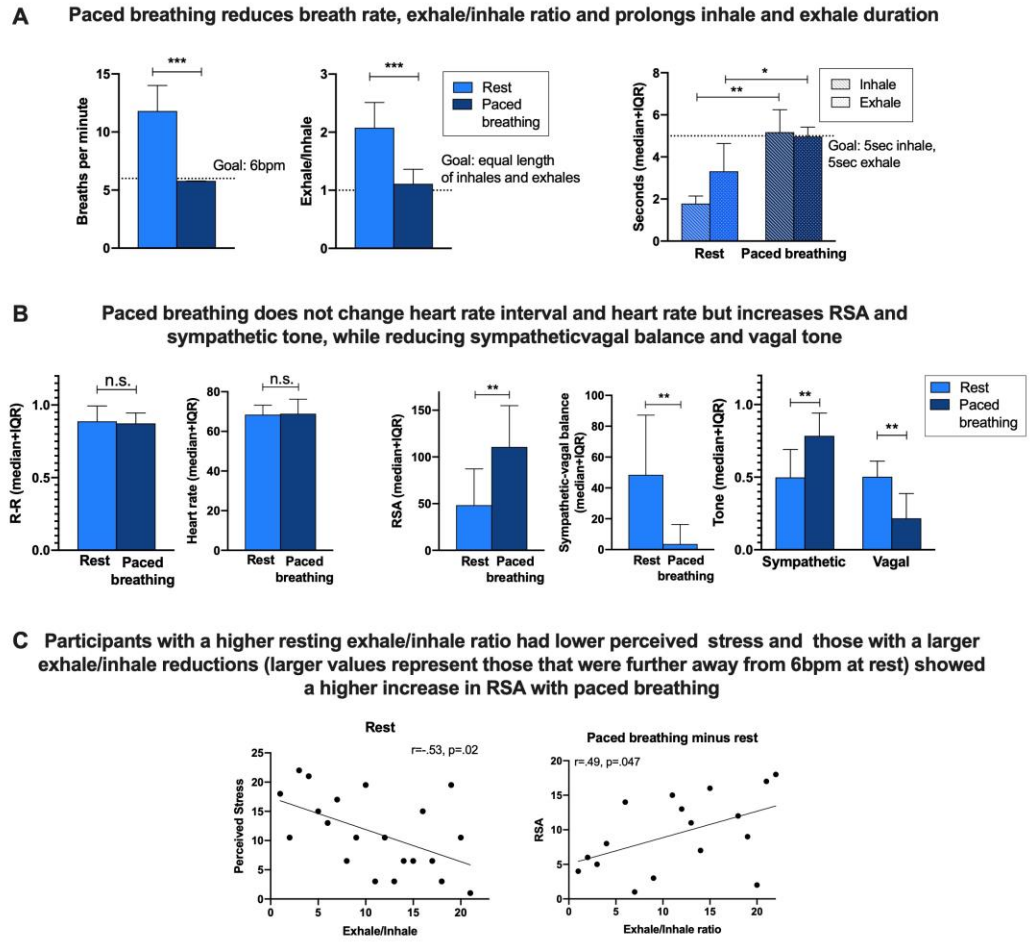
Support: Alzheimer's Research and Prevention Foundation

Title: Breathing at 6 breaths per minute modulates autonomic tone in women at risk for Alzheimer's disease

Authors: *B. KRAUSE-SORIO[1], P. M. MACEY[2], P. SIDDARTH[1], K. T. LAIRD[1], K. NARR[3], H. LAVRETSKY[1];
[1]Psychiatry, [2]Sch. of Nursing, [3]Brain Mapping Ctr., Univ. of California Los Angeles, Los Angeles, CA

Abstract: Cardiovascular risk factors in aging populations increase the risk for Alzheimer's disease (AD). Breath and heart rate are linked and influence one another. Breathing exercises, including breathing at 6 breaths per minute (bpm) can calm the autonomic nervous system (ANS) and modulate cardiac function. We investigated whether five minutes of breathing at 6bpm affected cardiac and ANS measures in 23 older women with cardiovascular risk factors (mean age=68.91, SD=10.8). Participants completed the perceived stress scale and underwent respiratory and electrocardiogram (ECG) recording for five minutes at rest and slow breathing each. BioPac equipment and Acqknowledge software 5.0 were used to compute exhale/inhale ratio, R-R intervals, heart rate (HR), sympathetic-vagal balance, respiratory sinus arrhythmia (RSA) and sympathetic and vagal tones. We used non-parametric Spearman's correlation coefficients and paired-samples Wilcoxon ranked tests (rest vs. slow breathing). Perceived stress correlated negatively with resting exhale/inhale ratio (rho=-.53, p=.02). Breath rate significantly slowed with paced breathing (Z=-4.14, p<.001). R-R interval and HR remained stable (ps>.09), while RSA increased (Z=3.33, p=.001) and sympathetic-vagal balance decreased with paced breathing (Z=2.9, p=.004). Sympathetic tone increased (Z=2.98, p=.003) and vagal tone decreased (Z=-2.98, p=.003). The change in exhale/inhale correlated with RSA change, i.e.

participants who showed the largest reduction during slow breathing, increased the most in RSA (rho=.49, p=.047).
In sum, older women with risk factors associated with AD, show larger exhale/inhale ratios with lower perceived stress. Breathing at 6bpm rendered heart rate unchanged but reduced vagal activity, while increasing sympathetic tone. Higher resting exhale/inhale corresponded to increased vagal tone during slow breathing. Slow breathing may not benefit this at risk group. Training and longer interventions, as well as a control group are required to optimize vagal activity in this population.



Disclosures: B. Krause-Sorio: None. **P.M. Macey:** None. **P. Siddarth:** None. **K.T. Laird:** None. **K. Narr:** None. **H. Lavretsky:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.15/X29

Topic: F.04. Stress and the Brain

Support: BasFin "Technostress in Organisationen"

Title: Investigating technostress from a neurobiological perspective: Results of a neurois research program with a focus on field studies

Authors: R. RIEDL, ***T. FISCHER**;
Univ. of Applied Sci. Upper Austria, Steyr, Austria

Abstract: Neuro-Information-Systems (NeuroIS) relies on neuroscience and neurophysiological knowledge and tools to better understand the development, use, and impact of information and communication technologies (ICT) (Riedl, Fischer, & Léger, 2017; Riedl & Léger, 2016). A major topic in NeuroIS research is *technostress*, defined as stress that results from both the use of ICT and the pervasiveness and expectations of ICT use in society in general (Riedl, 2013). In previous technostress research, a strong focus on self-report measurement (e.g., survey) is observable (Fischer & Riedl, 2017), which is problematic as pointed out by Riedl (2013, p. 19), who writes: “[B]efore humans even begin to consciously perceive negative effects of stress ⋯, about which they could give an introspective account in self-reports, it is often the case that biological systems ⋯ have already started to act in the body...” Against this background, in our research program on technostress we use neurophysiological tools and measures, in particular those related to measurement of autonomic nervous system activity and we concentrate on the investigation of technostress in the field (in organizational environments) as most existing studies were conducted in laboratory settings. In a case study with 16 participants, we tracked individual stress over a period of three weeks based on blood pressure and heart rate variability. While we did not find any significant changes in blood pressure due to stress, we found changes in sympathetic (represented by LF/HF ratio of heart rate) and parasympathetic activity (represented by RMSSD of heart rate). In a recent field experiment, we investigated the effect of technological unreliability (e.g., non-availability of websites) on heart rate. A major result of this preliminary evidence is that we observed time-related changes, in particular habituation to stressors. It will be rewarding to see what insight future neurophysiological research will reveal on technostress. Fischer, T., & Riedl, R. (2017). Technostress Research: A Nurturing Ground for Measurement Pluralism? *Communications of the Association for Information Systems*, *40*(1), 375-401. Riedl, R. (2013). On the Biology of Technostress: Literature Review and Research Agenda. *DATA BASE for Advances in Information Systems*, *44*(1), 18-55. Riedl, R., Fischer, T., & Léger, P.-M. (2017). A Decade of NeuroIS Research: Status Quo, Challenges, and Future

Directions. In AIS (Ed.), *Proceedings of ICIS 2017.* Riedl, R., & Léger, P.-M. (2016). *Fundamentals of NeuroIS: Information Systems and the Brain* (1st ed. 2016). *Studies in Neuroscience, Psychology and Behavioral Economics*. Berlin, Heidelberg: Springer.

Disclosures: R. Riedl: None. **T. Fischer:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.16/X30

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: AMED under grant No. JP16bk0104016
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JSPS KAKENHI Grant No. JP1710083

Title: Abnormal dendrite and synapse formation in neurons differentiated from psychiatric disorder patient-derived induced pluripotent stem cells with copy number variation of PCDH15 and RELN

Authors: *T. ISHII[1,3], M. ISHIKAWA[1], K. FUJIMORI[1], T. MAEDA[1,4], I. KUSHIMA[4], Y. ARIOKA[4], D. MORI[4], B. YAMAGATA[2], S. NIO[2], T. A. KATO[5], S. KANBA[5], M. MIMURA[2], N. OZAKI[4], H. OKANO[1];
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Abstract: Although useful *in vitro* models of psychiatric disorders such as bipolar disorder (BP) and schizophrenia (SCZ) are required for pathological analysis and drug discovery, it is difficult to establish good *in vitro* models because of the heterogeneity of these disorders. In the present study, in attempt to establish *in vitro* models recapitulating the characteristics of these disorders, we performed the phenotype analysis using patient-derived induced pluripotent stem cells (iPSCs). To overcome the phenotypic variations, we focused on the patients with copy number variations (CNVs) which are expected to be highly contributive factors affecting the onset and treatment resistance. Thus, we established iPSCs from BP and SCZ patients with novel CNVs: two BP patients with *PCDH15* heterozygous exonic deletion and one SCZ patient with *RELN*

heterozygous exonic deletion. We differentiate iPSCs into neurons by two methods: dual-SMAD inhibition and overexpression of transcriptional factors. Immature neurons from patient-derived iPSCs induced by dual-SMAD inhibition showed abnormalities of neurite extension. Then, we differentiated iPSCs into both glutamatergic and GABAergic mature neurons separately and efficiently by overexpressing different set of transcriptional factors. We performed immunocytochemical analysis and found that both types of induced neurons from both patients-derived iPSCs exhibited similar phenotypes in dendrite and synapse formation, which are similar to the previously reported findings observed in the postmortem brains. These results suggest that our *in vitro* model may reflect general phenotypes of these disorders. Now, we are investigating the genotype-phenotype causal relationship using genome-edited isogenic iPSCs.

Disclosures: **T. Ishii:** A. Employment/Salary (full or part-time):; T.I. are employed Sumitomo Dainippon Pharma. Co., Ltd. **M. Ishikawa:** None. **K. Fujimori:** A. Employment/Salary (full or part-time):; K.F are employed by Sumitomo Dainippon Pharma Co., Ltd. **T. Maeda:** None. **I. Kushima:** None. **Y. Arioka:** None. **D. Mori:** None. **B. Yamagata:** None. **S. Nio:** None. **T.A. Kato:** None. **S. Kanba:** None. **M. Mimura:** None. **N. Ozaki:** 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.; N.O. are supported by a research grant from Sumitomo Dainippon Pharma Co., Ltd. **H. Okano:** A. Employment/Salary (full or part-time):; H.O. is a founding scientist of SanBio Co. Ltd. and K Pharma Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; H.O. are supported by a research grant from Sumitomo Dainippon Pharma Co., Ltd.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.17/X31

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: CIHR
Pfizer

Title: Emotional control in bipolar disorder type 1: An mvpa analysis of fMRI data

Authors: *F. KONDO[1,3], J. C. WHITEHEAD[1,3], F. CORBALÁN[3], S. BEAULIEU[2,3], J. L. ARMONY[2,3];
[1]Integrated Program in Neurosci., [2]Dept. of Psychiatry, McGill Univ., Montreal, QC, Canada; [3]Douglas Mental Hlth. Univ. Inst., Verdun, QC, Canada

Abstract: Background: Bipolar disorder type-I (BD-I) patients are known to show emotion regulation abnormalities. In a previous fMRI study using an explicit emotion regulation paradigm, we compared responses from 19 BD-I patients and 17 matched healthy controls (HC). A standard GLM-based univariate analysis revealed that BD patients showed increased activations in VLPFC when instructed to decrease the emotional response elicited by neutral images indicating BD patients engage this region even when emotion regulation is not necessary. Also, BD patients showed sustained amygdala response to all negative images regardless of instruction. **Methods:**We reanalyzed explicit emotion regulation data using a multivariate pattern recognition approach, as implemented in PRONTO. The original experimental paradigm consisted of a full 2 × 2 factorial design, with valence (*Negative/Neutral*) and instruction (*Look/Decrease*) as within subject factors. **Results:**The multivariate models were able to accurately classify different task conditions when HC and BD were analyzed separately (63.24 % - 75.00 %, p =0.001 to 0.012). In addition, the models were able to correctly classify HC vs BD with significantly above-chance accuracy for "Decrease" conditions (58.61 % - 60.84 %, p =0.003 to 0.014). Also, the results for HC vs BD classification demonstrated an involvement of several frontal and occipital regions, as well as other cortical regions, including inferior parietal lobe, to the classification.**Conclusion:**Our multivariate analysis successfully reproduced some of the results obtained in our previous univariate analysis, confirming that these findings are not dependent on the analysis approach. In particular, both types of analysis suggest that there is a significant neural pattern difference between conditions within each subject group, and also between HC and BD during "Decrease" conditions, indicating that BD shows distinct patterns of neural activity from HC when engaging in cognitive control.

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Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.18/X32

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: JSPS KAKENHI Grant Number 19K08049

Title: Gamma band auditory steady-state responses in bipolar disorder patients

Authors: *N. ORIBE[1], Y. HIRANO[2], S. HIRANO[3], T. ONITSUKA[3], T. UENO[4];
[1]Hizen Psychiatric Ctr., Saga, Japan; [2]Neuropsychiatry, [3]Kyushu Univ., Fukuoka, Japan; [4]Hizen Psychiatry Ctr., Kanzaki-Gun, Japan

Abstract: Gamma band auditory steady state response (ASSR) especially to 40Hz stimuli have been reported to be consistently abnormal and considered to be a robust biomarker in schizophrenia patients. However, the ASSR deficits in patients with bipolar disorder have not been investigated enough. We previously reported abnormal ASSR to 30, 40 and 80 Hz stimuli in Patients with bipolar disorder using magnetoencephalography. In the current study, we measured ASSR responses in bipolar disorder patients (BP, N=13), as well as in patients with major depressive disorder (DP, N=5) and healthy control subjects (HC, N=41) while presenting click trains varying in rate of stimulation (20, 30, 40 and 80 Hz) using electroencephalography(EEG). EEG-evoked power and phase locking were obtained in response to each stimulation frequency.
BD showed significant reduction in phase locking to the 40Hz stimuli compared with HC while DP showed intact responses both in phase locking and evoked power to the 40Hz stimuli. There were no significant group differences in responses to other frequency bands.Our findings suggest that 40 Hz phase locking are impaired in Bipolar disorder.Patients with major depressive disorder didn't show ASSR deficits in our sample.Further investigation with larger samples will be required to elucidate these results.

Disclosures: N. Oribe: None. **Y. Hirano:** None. **T. Onitsuka:** None. **T. Ueno:** None. **S. Hirano:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.19/X33

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Grant-in-Aid for Young Scientists 18K15521
Takeda Pharmaceutical COCKPI-T 2018

Title: Development of induced pluripotent stem cell model of bipolar disorder derived from an Okinawan pedigree with a potential genetic component

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Abstract: Background. Bipolar disorder is a psychiatric disease characterized by high genetic heterogeneity. It is believed that there is a genetic component to bipolar disorder, but genomic variations that strongly and directly contribute to bipolar disorder are not still specified, and the pathophysiology of bipolar disorder is also not fully understood. Recently, patient-derived induced pluripotent stem cells (iPSCs) with genetic variations having large effects on the development of neuropsychiatric diseases are expected to be cellular disease models. However, iPSC disease models with specific genomic causes of bipolar disorder remain absent. Here, to establish novel iPSC disease models of bipolar disorder with a strong genetic component, we surveyed pedigrees with multiple patients of bipolar disorder in Okinawa, the southern islands in Japan, and performed comprehensive genomic analysis and generated iPSC lines.
Results. We found a large family with an autosomal dominant inheritance pattern of bipolar disorder and recurrent depressive disorder in an isolated island of Okinawa. We obtained informed consent from participants and collected blood samples of 8 affected and 8 unaffected individuals. Parametric linkage analysis detected a significant linkage peak in a chromosome region which previous studies repeatedly reported link to bipolar disorder and depression. Whole genomic sequencing-based haplotype phasing determined an extremely rare haplotype shared among affected individuals of the pedigree in the chromosomal linkage region. We focused on a candidate gene in the affected haplotype and identified the characterized localization of the gene in the brain. We generated iPSC lines from affected and unaffected individuals of the pedigree and differentiated iPSCs into neurons. We are now investigating the phenotype of the iPSC-derived neurons and the relationship between the genomic variant and the neuronal phenotype.
In summary, we identified the affected haplotype and candidate variants which have the potential to contribute to bipolar disorder and induced iPSC-derived neurons with the genetic component. Our work could be expected to establish the cellular model of bipolar disorder for various applications.
The study was approved by the Research Ethics Committee of the University of the Ryukyus and all participating institutes.

Disclosures: G. Takamatsu: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Takeda Pharmaceutical. **K. Yanagi:** None. **J. Lee:** None. **Y. Manome:** None. **C. Hara-Miyauchi:** None. **K. Koganebuchi:** None. **K. Hattori:** None. **M. Hasegawa:** None. **M. Isa:** None. **D. Dimitrov:** None. **H. Tomoko:** None. **T. Kondo:** None. **T. Takahashi:** None. **H. Kunugi:** None. **H.J. Okano:** None. **R. Kimura:** None. **T. Kaname:** None. **M. Matsushita:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.20/X34

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH: R01MH104261
ONR N00014-12-1-0366
NIDA: U01DA043098
Hope for Depression Research Foundation
Pritzker Neuropsychiatric Research Consortium

Title: Analysis of commonly used reference genes in the frontopolar cortex in schizophrenia and bipolar disorder

Authors: *A. MEDINA[1], E. HUGHES[2], W. E. BUNNEY[3], R. MYERS[4], A. SCHATZBERG[5], J. D. BARCHAS[6], H. AKIL[7], S. J. WATSON, Jr.[7];
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Abstract: Quantitative reverse transcription PCR (qRT-PCR) is frequently used to demonstrate changes in gene expression levels in a wide range of conditions. A normalization step is routinely included, preferably by using multiple stably expressed reference genes, also known as housekeeping genes. Some of those genes, such as beta-actin (ACTB) or ubiquitin (UBC) are universally considered as unvarying and used for the normalization step. However, it is important to acknowledge the inherent biological variability of each set of samples and the possible effect of disease on the genes selected. In this study, we aim to determine what the best set of reference genes would be for the analysis of gene expression in the human Frontopolar cortex in healthy control subjects compared to bipolar disorder (BPD) and schizophrenic subjects (SZ).
Methods: Human brain blocks from the Frontopolar cortex of 23 controls, 24 schizophrenics, and 21 bipolar disorder subjects were obtained from the Brain Donor Program at the University of California, Irvine by agreement with the Pritzker Neuropsychiatric Consortium. The subjects included in the schizophrenic and bipolar disorder groups met diagnostic criteria from the Diagnostics and Statistical Manual of Mental Disorders (DSM-V). In the control group, there was no evidence of psychiatric or neurological disorders. Variables accounted for include gender, age and postmortem interval. All subjects used in the study had tissue pH above 6.5 and

agonal factor scores (AFS) of zero. Fresh frozen blocks of tissue averaging 500 mg were dissected from the frontopolar region of each subject and processed for RNA extraction to be used for gene expression studies. We used TaqMan® microfluidic cards to perform qPCR in a Viia™7 machine for evaluation of the gene expression profiles of a set of 12 commonly used reference genes: 18s, ACBT, B2M, HPRT1, GUSB, HMBS, IPO8, PGK1, RPLP0, TBP, TFRC, UBC. ExpressionSuite® software version 1.1 was used to analyze the results.
Results: ExpressionSuite® software allows the evaluation of different quality control measurements for the endogenous controls and targets run in a microfluidic card. After looking at parameters such as standard deviation, Ct max, and Cq confidence values, our results show that several commonly used reference genes are not ideal for normalization of gene expression in our samples. Of twelve genes tested, only five were a good fit for our study, as the other seven showed high variability, especially in the control samples.
We suggest that a careful selection of housekeeping genes appropriate to the sample being used is a fundamental first step before proceeding with gene expression studies using qPCR.

Disclosures: A. Medina: None. **E. Hughes:** None. **W.E. Bunney:** None. **R. Myers:** None. **A. Schatzberg:** None. **J.D. Barchas:** None. **H. Akil:** None. **S.J. Watson:** None.

Poster

508. Mood Disorders: Depression and Bipolar Disorders: Clinical Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 508.21/X35

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH R01MH093420

Title: Differentiating young depressed adults at high risk for developing bipolar disorder from those at low risk: A machine learning approach

Authors: *J. CHA, A. ANAND;
Cleveland Clin., Cleveland, OH

Abstract: Introduction:Identifying major depressive disorder (MDD) patients who are at high risk (HRMDD)(indicated by subthreshold symptoms or family history) for developing bipolar disorder (BD) is a critical diagnostic and treatment issue. This study aims to use brain imaging data from an fMRI activation task to construct a predictive model to classify three groups: BD, HRMDD, and low risk MDD (LRMDD).
Methods:Subjects:This study recruited BD and MDD participants ages 15-30 years who were medication-free for at least 2 weeks from the outpatient psychiatry clinic at the Cleveland Clinic and by advertisement. The final analyses included 94 subjects: 20 BPD (bipolar I and bipolar II), 33 HRMDD, and 41 LRMDD. Imaging:We used an Emotion Go/No-go fMRI activation task

paradigm. We conducted the analysis in AFNI. Beta images (contrast images) were used by computing the difference between NoGo vs. Go condition: Happy face inhibition (Happy NoGo vs. Neutral Go), Fear face inhibition (Fear NoGo vs. Neutral Go), and Emotional Face Inhibition ((Happy NoGo + Fear NoGo) vs. Neutral Go). Machine Learning Analysis: We used the random forest algorithm in R statistical software. Firstly, using the whole-brain beta images, we extracted 116 ROI-wise average values from using the AFNI built-in atlas.For feature selection, we performed Recursive Feature Elimination (RFE) with ten-fold cross validation (CV) for all subjects via random forest approach to identify ROIs which contributed the most to classify the groups. The predictive model was trained based on the training set with the ten-fold CV and applied to the test set for prediction. By comparing the predicted and true labels, we computed the area under the receiver operating characteristics (ROC) curve (AUC).
Results: A. HRMDD vs LRMDD: Happy face inhibition (0.80 AUC and 0.70 accuracy); Fear face inhibition (0.68 AUC and 0.68 accuracy); and Emotional Face Inhibition (0.80 AUC and 0.70 accuracy). B. (BPD+HRMDD) vs LRMDD: Happy face inhibition (0.76 AUC and 0.68 accuracy), Fear face inhibition (0.68 AUC and 0.67 accuracy), and Emotional Face Inhibition (0.72 AUC and 0.68 accuracy). C. BPD vs MDD(HRMDD +LRMDD): Happy face inhibition (0.81 AUC and 0.79 accuracy), Fear face inhibition (0.74 AUC and 0.82 accuracy), and Emotional Face Inhibition (0.74 AUC and 0.79 accuracy).
Conclusions:The classification approach with machine learning techniques applied to fMRI task-induced activation data may provide a method for diagnostic classification of MDD subjects at high and low risk for BPD. This method may also be useful to differentiate BPD from MDD.

Disclosures: J. Cha: None. **A. Anand:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.01/X36

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Bioenergetic and behavioral impacts of ketamine and lithium combinatorial treatment in a state of antidepressant resistance

Authors: *J. PRICE[1], B. A. MORATH[1], K. BUTTERS[1], M. A. FRYE[3], S. MCGEE[4], S. J. TYE[2];
[2]Psychiatry & Psychology, [1]Mayo Clin., Rochester, MN; [3]Integrative Biol. and Physiol., UCLA, Los Angeles, CA; [4]Deakin Univ., Waurn Ponds, Australia

Abstract: Background: The potential of ketamine's efficacy with adjunctive treatments in treatment-resistant depression is still relatively unexplored. Lithium is a common adjunctive treatment for refractory depression, as well as a mood stabilizer for bipolar disorder. Its

molecular mechanisms overlap with those of ketamine and it has been shown to enhance the duration of ketamine's efficacy in rodents modeling depression, even when both treatments are administered at subclinical doses (Duman, 2014). Here, we investigate ketamine and lithium's synergistic effects in a rodent model of antidepressant treatment resistance.
Methods: To establish an antidepressant-resistant phenotype, male Wistar rats were administered adrenocorticotropic hormone (ACTH; 100ug/day, 14 days). Rats were subsequently treated with ketamine (10mg/kg; 2 days; n=12), lithium (37mg/kg; 2 days; n=12), ketamine+lithium (n=12), or control vehicle saline (0.9%; n=12). Rats were subjected to open field (6 minutes) and forced swim tests (6 minutes). Thirty minutes after behavioral testing, rats were euthanized, and cardiac blood and brain tissue were immediately collected. Enzyme-linked immunosorbent assays (ELISAs) were performed to detect mammalian target of rapamycin (mTOR), glycogen synthase kinase-3ß (GSK3ß), and glutamate ionotropic receptor AMPA 1 (GRIA1) concentrations.
Results: ACTH-pretreated rats receiving ketamine+lithium expressed significantly reduced immobility in the forced swim test compared to ACTH-controls ($p<0.05$), unlike rats receiving ACTH+ketamine or ACTH+lithium. Open field testing did not reveal significant pre-existing differences in locomotor activity between groups. Rats treated with ketamine+lithium had higher expression of peripheral mTOR and central GRIA1 than rats receiving ketamine or lithium alone, as well as higher peripheral insulin than all other groups.
Conclusions: These results suggest a synergistic capability of combinatorial ketamine and lithium treatment mediated by enhanced effects on cellular protein signaling and plasticity. The cumulative impact of ketamine+lithium was effective in promoting greater mTOR, GRIA1, and insulin as compared to rats treated with ketamine or lithium alone. Taken together, the elevation of these factors resulted in a greater antidepressant-like effect as reflected in the forced swim test.

Disclosures: J. Price: None. **B.A. Morath:** None. **K. Butters:** None. **M.A. Frye:** None. **S. McGee:** None. **S.J. Tye:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.02/X37

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Assessment of rapid antidepressant effects of ketamine in animal model

Authors: R. MEDAPATI, J. TADIPARTHI, N. GANUGA, G. RAMALINGAYYA, P. JAYARAJAN, *K. MUDIGONDA, R. NIROGI;
Suven Life Sci. Ltd, Hyderabad, India

Abstract: Current existing pharmacotherapies for treating major depressive disorders (MDD) generally take several weeks to months to exert their full therapeutic effects. Clinical evidences showed that ketamine, a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist exert rapid antidepressant effects. The antidepressant effect of ketamine was evaluated in dominant submissive assay. Briefly, animals were food-deprived overnight prior to testing. Habituation of the animal to the apparatus and milk was carried out during the first week (one week). Selection of dominant and submissive pair was carried out during the second week (one week). The animals were randomized based on the dominance levels. Both the dominant and submissive animals of the control group were treated with vehicle. For the remaining groups, submissive animals were treated with ketamine or imipramine or fluoxetine. In the control treatment group, dominance levels remained unchanged during the entire course of the study. In the ketamine treatment group, dominance levels decreased significantly from the 3rd day of the treatment. Significant effects of imipramine or fluoxetine was observed only during the 3rd week of treatment. Based on the results, it can be concluded that ketamine exerts its antidepressant activity rapidly than the current conventional treatments. There is a need of thorough research for finding out the exact mechanism of action of ketamine's antidepressant effects.

Disclosures: R. Medapati: A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **J. Tadiparthi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **N. Ganuga:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **G. Ramalingayya:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **K. Mudigonda:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time):; Suven Life Sciences Ltd..

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.03/X38

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Maternal separation and prolonged exposure to ketamine did not alter maternal behavior in rats

Authors: *E. L. RICCI[1], B. RIBEIRO[2], L. PANTALEON[2], J. Z. MAGALHÃES[3], G. ABREU[4], A. R. FUKUSHIMA[4], C. MUNHOZ[2], M. RIBEIRO[2], H. S. SPINOSA[4];
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Abstract: Postpartum depression is a multifactorial mental disorder that affects 1 in 7 women worldwide and it is an important public health problem since affects both mother and child's health. There are pharmacotherapies available for the treatment of this disease, but many of these medications can affect the child through breastfeeding. Likewise, there are several women that do not respond to those therapies, which make it urgent the development of more effective, faster-acting and with less side effects medications. Recent studies have shown that ketamine has a promising therapeutic potential for treatment of depression, due to its rapidly response, low toxicity, and few side effects. However, there is no established dose and route of administration for ketamine's use as an antidepressant. Thus, the aim of this study was to evaluate the effects of maternal separation as a postpartum depression model and of prolonged exposure to ketamine in lactating rats. Twenty-four dams were divided into three groups: group A - control; group B - maternal separation; and group C - maternal separation + ketamine 10 mg/kg, n=8 animals/group. Groups B and C were induced to postpartum depression through the maternal separation model for 10 days, from lactating day 2 to 12, which was previously validated through the forced swim test. Group C was also treated with 10 mg/kg of ketamine intraperitoneal during all lactation period. On lactating day 5 and 6 it was performed the maternal behavior and the maternal aggressive behavior tests, respectively. The parameters evaluated on the maternal behavior test were: latency to retrieve the first 4 pups, latency to group all pups in the nest, percentage of dams that group all pups in the nest, total time of pup-grooming, total time of self-grooming, latency to full maternal behavior and percentage of dams that displayed the full maternal behavior. The parameters evaluated on the maternal aggressive behavior were: total time of social interaction with the intruder, total time that the intruder spends sniffing the offspring, frequency of boxing, latency to the first fight, number of fights, total time of maternal behavior and total time of self-grooming. The results showed no differences between groups in all parameters evaluated, which indicates that neither the maternal separation model nor the ketamine exposure was able to alter the maternal behavior of these animals

Disclosures: E.L. Ricci: None. **B. Ribeiro:** None. **L. Pantaleon:** None. **J.Z. Magalhães:** None. **G. Abreu:** None. **A.R. Fukushima:** None. **C. Munhoz:** None. **M. Ribeiro:** None. **H.S. Spinosa:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.04/X39

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Naltrexone attenuates the antidepressant-like effects of ketamine in C57B/6 mice

Authors: *F. ZHANG, R. RICE, J. H. PORTER, A. ANDRADE, S. MANICKA, J. LANE; Psychology, Virginia Commonwealth Univ., Richmond, VA

Abstract: Ketamine has been shown to produce both rapid and prolonged antidepressant effects in depressed patients; however, the underlying mechanisms mediating these antidepressant effects remains undetermined. Ketamine's antagonism of glutamatergic NMDA receptors has been the focus of much research; however, other mechanisms may be responsible for ketamine's antidepressant effects as ketamine is known to interact with several other neurotransmitter systems, including opioid receptors. Recently, Williams et al. (2018) reported that the opioid receptor antagonist naltrexone attenuated ketamine's low dose (0.5 mg/kg, iv) antidepressant effect in depressed patients. Interestingly, the dissociative effects of ketamine were not blocked by naltrexone. The authors suggested that opioid system activation is necessary for ketamine's acute antidepressant to be evident. The current study explored this possibility by testing C57BL/6 mice in a differential-reinforcement-of-low-rate (DRL) 72 s operant task. In the DRL assay, animals are required to wait for a specified length of time (e.g., 72 s) between lever responses to receive a reinforcer. Drugs with clinical efficacy as antidepressants typically increase the number of reinforcers received and decrease the number of responses emitted. The DRL 72 s task has high predictive validity for screening antidepressant drugs, and is less vulnerable to false positives (e.g. psychostimulants). Ketamine (32 mg/kg) produced a significant increase in the number of reinforcers received as compared to vehicle. Next, the mu opioid receptor antagonist naltrexone (1, 2, and 4 mg/kg doses) was tested alone and in combination with 32 mg/kg ketamine. Naltrexone alone did not produce any significant increases in reinforcers. However, when tested in combination with 32 mg/kg ketamine, naltrexone produced a significant reduction of ketamine's antidepressant-like effects at 2 mg/kg, but not at 1 or 4 mg/kg doses. Thus, naltrexone's effects on ketamine's antidepressant-like effects produced an inverted U-shaped function. Additional testing is being conducted to determine if this inverted U-shaped function can be replicated. These results tentatively support the conclusion by Williams et al. (2018) that opioid system activation may be necessary for ketamine's acute antidepressant effects.

Disclosures: F. Zhang: None. **R. Rice:** None. **J.H. Porter:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.05/X40

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Evaluating the antidepressant-like effects of ketamine, its isomers, and (2R,6R)-hydroxynorketamine (HNK) in C57B/6 mice

Authors: *J. H. PORTER, F. ZHANG, J. E. PRICE, M. K. SHEARER, E. POTTANAT, R. RICE;
Psychology, Virginia Commonwealth Univ., Richmond, VA

Abstract: The monoamine hypothesis inadequately explains the delay of therapeutic effects of currently available antidepressants. Recently, there has been an increased focus on the role of glutamatergic mechanisms underlying depression; following the demonstration that a single, subanesthetic dose of ketamine (0.5 mg/kg iv) produced a rapid and long lasting (3 days) improvement of depressive symptoms (Berman et al 2000; Hillhouse and Porter 2015). Preclinical research also has reported antidepressant-like effects with ketamine treatment in several assays (Maeng et al., 2008; Zhou et al., 2014), but ketamine's abuse liability and psychotomimetic side-effects limit its clinical use. In addition to the (R)-ketamine and (S)-ketamine isomers, it was recently postulated that the ketamine metabolite, (2R,6R)-hydroxynorketamine (HNK) may be important for ketamine's antidepressant effects (Zanos et al., 2016). The observed antidepressant-like actions of HNK were independent of NMDAR antagonism and it lacked ketamine-related side effects. The current study examined the antidepressant-like effects of ketamine, its isomers, and HNK in C57BL/6 mice in a differential-reinforcement-of-low-rate (DRL) 72 s operant task. In the DRL assay, animals are required to wait for a specified length of time (e.g., 72 s) between lever responses to receive a reinforcer. Drugs with clinical efficacy as antidepressants typically increase the number of reinforcers received and decrease the number of responses emitted. The DRL 72 s task has high predictive validity for screening antidepressant drugs, and is less vulnerable to false positives (e.g. psychostimulants). Ketamine (32 mg/kg) and the S-isomer (17.8 and 32 mg/kg)produced a significant increase in the number of reinforcers received as compared to vehicle. The (R) isomer (32 mg/kg) did not increase the number of reinforcers. HNK (56 mg/kg) also failed to increase the number of reinforcers. Thus, while ketamine and (S)-ketamine displayed an antidepressant-like profile in the DRL 72 s assay, (R)-ketamine and HNK did not. These results different from other preclinical assays of antidepressant-like behavior (e.g. forced swim test).

Disclosures: J.H. Porter: None. **F. Zhang:** None. **R. Rice:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.06/X41

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Effects of ketamine and (2R-6R)-hydroxynorketamine (HNK) on cognition: A role for the nucleus reuniens?

Authors: *R. RICE[1], F. ZHANG[1], P. GOSWAMEE[2], R. MCQUISTON[2], J. H. PORTER[1]; [1]Psychology, [2]Dept Anat/Neurobiol, Virginia Commonwealth Univ., Richmond, VA

Abstract: Major depressive disorder is the most common mental disorder worldwide. The U.S. alone has a greater than 16% lifetime prevalence rate for depression. Here, treatment costs and an estimated loss in productivity cause an annual $83 billion socioeconomic burden. More efficacious pharmacological treatments might attenuate this burden. After the demonstration that a single, subanesthetic dose of ketamine (0.5mg/kg i.v.) produced a rapid and relatively long-lasting (3 days) improvement of depressive symptoms, there is increased focus on glutamatergic mechanisms for the treatment of MDD. Animal research also has reported antidepressant-like effects with ketamine, but these promising findings are limited by ketamine's aversive side effects. Fortunately, the antidepressant-like actions of (2*R*,6*R*)-hydroxynorketamine (HNK), a ketamine metabolite, appeared to lack side effects associated with ketamine treatment (e.g. psychomimetic effects). Similar to others, we saw ketamine exert antidepressant-like effects in rodents as measured by the forced-swim test. To assess potential cognitive-effects of these compounds, we measured spontaneous alternation in a T-maze after treatment with racemic ketamine and HNK (both 10 mg/kg and 32 mg/kg; both with 5-minute and 24-hr pretreatments) on adult male C57BL/6 mice. Results indicate that ketamine significantly reduced alternations at both doses 5 minutes after treatment. Furthermore, these effects persisted for 24 hours at the higher ketamine dose of 32 mg/kg. Conversely, HNK (10 mg/kg and 32 mg/kg; 5 minute and 24-hour pretreatment) did not significantly differ from saline treatment. We hypothesize this effect is due in part to reduced neurotransmission in a thalamic nucleus; the midline thalamic nucleus reuniens (RE). RE acts as a structural and functional hub in the flow of information from the medial prefrontal cortex (mPFC) to the hippocampus. To assess whether ketamine reduced neurotransmission in the mPFC-RE pathway, we conducted whole-cell patch clamp electrophysiology in RE neurons in combination with optogenetic stimulation of mPFC afferents in brain slices of mice that received saline, ketamine, or HNK. Pilot electrophysiological data demonstrate that ketamine (32 mg/kg) reduces the strength of neurotransmission in the mPFC-RE pathway. Taken together, these results suggest that ketamine, but not HNK, can result in a cognitive deficiency that may arise due to alteration in the mPFC-RE neurocircuitry.

Disclosures: R. Rice: None. **F. Zhang:** None. **P. Goswamee:** None. **R. McQuiston:** None. **J.H. Porter:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.07/X42

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Evaluation of serotonin 2A receptor involvement in the antidepressant-like and abuse-related effects of ketamine

Authors: *T. M. HILLHOUSE[1], H. S. POPAL[2], C. MERRITT[2], S. E. CARLAN[2], K. A. WEBSTER[2], J. H. PORTER[2];
[1]Psychology & Neurosci., Weber State Univ., Ogden, UT; [2]Psychology, Virginia Commonwealth Univ., Richmond, VA

Abstract: The noncompetitive glutamatergic N-Methyl-D-aspartate (NMDA) receptor antagonist ketamine produces rapid and sustained antidepressant effects in treatment-resistant patients suffering from major depressive disorder (MDD). However, ketamine is considered to have high abuse liability due to dissociative and hallucinogenic effects, which are likely a result of NMDA receptor inhibition. There is some evidence that the abuse-related effects of ketamine are produced by activation of serotonin (5-HT) 2A receptors. Our study used a differential-reinforcement-of-low-rate (DRL) 72 s operant procedure and ketamine drug discrimination to determine the role of 5-HT2A receptors in the antidepressant-like and abuse-related effects of ketamine, respectively. The noncompetitive NMDA antagonists ketamine (5.6-18.0 mg/kg) produced antidepressant-like effects in the DRL 72 s procedure; whereas, the higher affinity noncompetitive NMDA antagonist MK-801 (0.1-0.18 mg/kg) produced a psychostimulant-like effect. The 5-HT2A receptor antagonist ritanserin (1.0 mg/kg) failed to block the antidepressant-like effects produce by 18.0 mg/kg ketamine, but reversed the psychostimulant-like effect of 0.18 mg/kg MK-801. To determine if ketamine was an antagonist at 5-HT2A receptors, as ketamine produced opposing behavioral effects as compared to MK-801 in DRL 72 s procedure and the behavioral effects of MK-801 were blocked by ritanserin, co-administration of the 5-HT2A agonist quipazine was used. Quipazine (5.6 mg/kg) failed to block the antidepressant-like effects of 10.0 mg/kg ketamine. Ketamine (7.5-20 mg/kg) produced full generalization in rats trained to discriminate 10.0 mg/kg ketamine in the drug discrimination paradigm. MK-801 (0.56-0.1 mg/kg) fully substituted for ketamine. The 5-HT2A agonist quipazine (0.32-3.2 mg/kg) and the 5-HT2A antagonist ritanserin (2.5-10.0 mg/kg) did not substitute for ketamine when administered alone and combination testing with ritanserin (10.0 mg/kg) did not block ketamine discrimination. These results suggest that 5-HT2A receptors do not play a significant role in ketamine's antidepressant-like or abuse-related effects.

Disclosures: T.M. Hillhouse: None. **H.S. Popal:** None. **C. Merritt:** None. **S.E. Carlan:** None. **K.A. Webster:** None. **J.H. Porter:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.08/X43

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Title: Evaluation of the antidepressant, anxiolytic, and locomotion effects of the N-methyl-d-aspartate (NMDA) receptor antagonist dextromethorphan in mice

Authors: *J. J. SAAVEDRA, S. C. HONEYCUTT, P. I. GARRETT, A. M. PETERSON, J. W. WHITE, T. M. HILLHOUSE;
Psychology & Neurosci., Weber State Univ., Ogden, UT

Abstract: Major Depressive Disorder (MDD) is among the most common disorders in the United States. The glutamatergic system is currently being evaluated as a novel pathway for treating MDD. For example, the N-methyl-d-aspartate (NMDA) receptor antagonist ketamine has produced rapid and sustained antidepressant effects in clinical trials. Other NMDA receptor antagonists have produced antidepressant-like effects in preclinical models, but have failed to produce similar antidepressant effects in clinical trials. It has become increasingly important to evaluate novel antidepressant drugs in several preclinical models to better understand the therapeutic potential of the drug. Dextromethorphan (DM) is a NMDA receptor antagonist that has produced antidepressant-like effects in the forced swim test (FST) and tail suspension test (TST); however, some studies have shown that DM can increase locomotor activity at a dose (30.0 mg/kg) that produces antidepressant-like effects. The present study sought evaluate the antidepressant-like, anxiolytic-like and behavioral effects of DM. The novelty-induced hypophagia (NIH) test was used to evaluate the rapid antidepressant-like and anxiolytic-like effects of DM. For the NIH test, mice are trained to drink a sweetened solution and then placed in a novel environment, which increases their latency to drink as compared to their home cage. Rapid antidepressants and anxiolytic drugs will decrease the latency to drink after acute administration; whereas, standard antidepressant drugs require repeated administration to reduce latency to drink. Acute administration of 20.0 mg/kg imipramine increased latency to drink. Interestingly, acute administration of 32.0 mg/kg DM significantly increased latency to drink as compared to saline. Neither drug significantly alter the volume of liquid consumed. A standard 60 min open field test was used to assess the effects of DM on locomotor activity. Treatment with 32.0 mg/kg DM did not significantly alter locomotor activity suggesting that the increased latency to drink in the NIH test was not a result of changes in locomotor behavior. These results suggest that while DM produces antidepressant-like effects in standard models of depression (i.e. FST and TST), DM does not produce rapid antidepressant-like effects in the NIH test. One possible explanation for these findings are that the antidepressant-like effects of DM have been attenuated by a sigma receptor antagonist suggesting that the antidepressant-like effects of DM are not produced by NMDA receptor antagonism. The inhibition of NMDA receptors produced by ketamine are thought to be responsible for the rapid antidepressant effects.

Disclosures: J.J. Saavedra: None. **S.C. Honeycutt:** None. **P.I. Garrett:** None. **A.M. Peterson:** None. **J.W. White:** None. **T.M. Hillhouse:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.09/X44

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH grant MH115396

Title: Corticosterone as a confounding factor in delineating mechanisms underlying ketamine's rapid antidepressant actions

Authors: *L. J. WEGMAN-POINTS, B. POPE, L. SEMKE, A. M. ZOBEL, E. WAUSON, V. DURIC, L.-L. YUAN;
Physiol. and Pharmacol., Des Moines Univ., Des Moines, IA

Abstract: Despite significant efforts, the mechanisms specific to ketamine's fast-acting antidepressant effects when administered in subanesthetic doses have yet to be identified. In our current study, we focused on the characterization of a previously observed surge in corticosterone (CORT) following a subanesthetic ketamine administration (10mg/ml). Blood and brain tissue collected at 1 hour post-injection of either saline, ketamine or (2R, 6R)-hydroxynorketamine (HNK), an active metabolite of ketamine, was analyzed for levels of circulating CORT. The levels of circulating CORT were ~ 4 fold higher in the ketamine-injected rats, when compared to saline controls and HNK treatment. This translated to an even more robust increase of CORT in the brain cortex. Interestingly, HNK did not elicit the spike in CORT seen with a ketamine injection. It is well established that ketamine, but not HNK, at antidepressant doses, induces side effects including locomotor deficits. To identify whether this increase in CORT was purely biochemical, or a behavioral response to the locomotor deficits, we removed the behavioral component by anesthetizing the rats before administering saline or ketamine. While under isoflurane sedation, the levels of circulating CORT 1 hour post-ketamine injection were consistent with those seen in anesthetized saline controls. This suggests that the increase in CORT levels is likely to reflect the increased stress of rats experiencing the locomotor deficit associated with a subanesthetic dose of ketamine. This increase in CORT release, virtually concurrent with ketamine administration in awake animals, could mask some of the mechanisms relevant to ketamine's rapid antidepressant effects, thus representing a potential confounding factor in this research.

Disclosures: L.J. Wegman-Points: None. **B. Pope:** None. **L. Semke:** None. **A.M. Zobel:** None. **E. Wauson:** None. **V. Duric:** None. **L. Yuan:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.10/X45

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Arkansas INBRE Faculty Recruitment

Title: Effect of ketamine on parvabumin interneurons in the prefrontal cortex and hippocampus during depression-like behavior in mice

Authors: *O. LAWLER[1], M. GAMES[1], V. MAGANA NAVAS[1], V. ARMENDARIZ CABRAL[2], K. MATA ARAUZ[3], K. ODELL[1], Q. WANG[1];
[1]Biol., [2]Chem., [3]Biochem., John Brown Univ., Siloam Springs, AR

Abstract: Major depressive disorder (MDD) is an illness characterized by lack of motivation, sadness, apathy, and suicidal thoughts and actions. While MDD is often attributed to a chemical imbalance in the brain, interneuron circuits may be a critical piece to understanding its complexity. MDD has been reported to impair parvalbumin (PV) interneuron activity under chronic stress (Hu, Wen et al. 2010; Czeh, Boldizsar et al. 2018). Previous research also suggests that ketamine has a fast-acting antidepressant effect. In mice, ketamine administration decreases immobility time during the forced swimming test (FST), an animal behavioral model of MDD (Zanos. et al. 2016). However, ketamine's effect on PV interneurons during FST is unclear. To understand ketamine's effects on PV interneurons in brain regions that are closely associated with MDD, we selectively examined the prefrontal cortex (PFC) and the hippocampus (HP). Vehicle (VEH, 0.9% saline) or ketamine (KET, 10 mg/kg) intraperitoneal injections were administered to 6-7-week-old male CD-1 mice one hour prior to FST. All mice were sacrificed by perfusion two hours after the onset of FST. Brain tissue slices were labeled with fluorophore-conjugated antibodies that recognized PV and Fos expression. PV interneurons and Fos puncta were quantified using ImageJ. As predicted, behavioral video analysis indicated a shorter immobility time in KET mice (n=3) compared to VEH (n=3) mice. Patterns of PV and Fos, however, varied between examined brain regions. Interestingly, in the PFC, quantification revealed no significant difference in the total number of PV interneurons in the lateral orbital cortex between groups. However, the percentage of dual-labeled neurons among all PV interneurons was significantly lower in KET mice. In the HP, the ventral CA1 displayed significantly higher numbers of PV- and dual-labeled neurons in KET mice, but no significant difference in the percentages of dual-labeled neurons among all PV interneurons. This region-specific pattern suggests that the antidepressant effect of ketamine may be mediated by differentially activated PV interneurons in these regions. Research is supported by The Arkansas IDeA Network of Biomedical Research Excellence (Faculty Recruitment) to QW.

Disclosures: **O. Lawler:** None. **M. Games:** None. **V. Magana Navas:** None. **V. Armendariz Cabral:** None. **K. Mata Arauz:** None. **K. Odell:** None. **Q. Wang:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.11/X46

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant MH113825

Title: Unique signaling of ketamine and 2R, 6R HNK in their rapid antidepressant actions

Authors: *R. THAPA[1], C. XU[2], X. CAI[1], S. YAN[3];
[1]Physiol., Southern Illinois Univ., Carbondale, IL; [2]Life Sci., Shaanxi Normal Univ., Xi'an, China; [3]Capital Med. Univ., Beijing, China

Abstract: Traditional antidepressant drugs generally take weeks and even months to ameliorate the conditions of people with depression. Ketamine, a noncompetitive NMDA receptor antagonist, exerts antidepressant actions in hours. However, its use is limited by its dissociative, psychotomimetic and other undesirable side effects. Recent studies have shown that the major metabolite of ketamine, 2R, 6R-HNK, exhibits antidepressant action but lacks unwanted side effects of ketamine. The mechanism of antidepressant action of 2R, 6R-HNK is not fully understood, especially the initial step and upstream signaling mediating the action of 2R, 6R-HNK on synaptic protein synthesis. In the current study, we observed that both ketamine and HNK enhanced fEPSPs and EPSCs at Schaffer collateral-CA1 (SC-CA1) synapses in acutely prepared hippocampal slices. MK-801, a selective NMDA receptor blocker, completely inhibited the action of ketamine but not 2R, 6R-HNK at SC-CA1 synapses. Ketamine but not 2R, 6R-HNK enhanced GluA1 Ser845 phosphorylation, and the action of ketamine but not 2R, 6R-HNK on synaptic transmission was abolished in GluA1 S845A knock-in mice. Using the optogenetic approach, we also explored the initiating signaling of 2R, 6R-HNK on excitatory synaptic transmission and synaptic protein synthesis in hippocampal CA1.

Disclosures: **R. Thapa:** None. **C. Xu:** None. **X. Cai:** None. **S. Yan:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.12/Y1

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: Stanford University, Department of Anesthesiology, Perioperative and Pain Medicine

Title: Ketamine produces a long-lasting enhancement of synaptic transmission

Authors: *G. JANG, B. MACIVER;
Anesthesiology, Perioperative and Pain Med., Stanford Univ. Sch. of Med., Stanford, CA

Abstract: Ketamine has recently been shown to improve major depressive disorder (MDD) in patients that are unresponsive to other forms of treatment. The antidepressant effect occurs rapidly, often following a single exposure, and can outlast the presence of the drug, often for several weeks. Current evidence suggests that the mechanism for this effect does not involve NMDA receptor antagonism. Little is known about other molecular targets for ketamine. The present study examined the effects of ketamine on synaptic transmission at glutamate and GABA synapses, to determine whether lasting effects can be produced by this drug. All procedures were approved by the Stanford University Animal Use Committee, male C57BL/6J mice weighing between 25-30 grams were used to prepare 400 µm thick coronal brain slices. We studied the effects of ketamine and its major metabolites (2R, 6R & 2S, 6S)-hydroxynorketamine by stimulating Shaffer-collateral axons while recording evoked responses from CA1 pyramidal neurons and GABA inhibitory interneurons. Ketamine produced three effects: 1) an acute depression of population spike amplitudes, 2) an enhancement of GABA-A fast and/or tonic inhibition, 3) a long-lasting increase in population spike amplitude. The long-lasting increase in amplitude was observed following drug washout and could last for over 8 hours. This effect was unlike other anesthetics that also produce an acute depression of population spike amplitudes, but do not produce long-lasting effects following washout. These effects were mimicked by the primary ketamine metabolite (2R, 6R)-hydroxynorketamine. Our results agree with previous studies showing that ketamine produces an acute depression of population spike amplitudes with an increase in GABA-mediated inhibition. This is the first report to demonstrate a long-lasting increase in excitability following washout of ketamine from the brain slice. We suggest this long-lasting effect could be related to the long-lasting antidepressant effects produced by ketamine and its (2R, 6R) metabolite. The (2R, 6R) metabolite is thought to be the active agent for ketamine-induced antidepressant effects.

Disclosures: G. Jang: None. **B. MacIver:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.13/Y2

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant NS084473 (D,J,)
BBRF young investigator award #26382 (C.S.K.)

Title: Antidepressant effects of s-ketamine through a reduction of functional I_h

Authors: *C. KIM, D. JOHNSTON;
The Univ. of Texas At Austin, Austin, TX

Abstract: Compelling evidence suggests that a single sub-anesthetic dose of ketamine exerts rapid and robust antidepressant effects. However, the cellular mechanisms underlying the antidepressant effects of ketamine remain unclear. We found that s-ketamine reduced dendritic but not somatic functional I_h of dorsal CA1 neurons in normal conditions. This effect was independent of NMDA receptors, barium-sensitive conductances (GIRK and IRK), and cAMP-dependent signaling. In the chronic unpredictable stress (CUS) model of depression, we found that s-ketamine reduced not only dendritic, but also the previously reported (Kim et al., 2018) CUS-induced upregulation of somatic functional I_h. Furthermore, s-ketamine normalized CUS-induced decreases in neuronal excitability and AMPA-mediated synaptic excitation at Shaffer collateral-CA1 synapses. Finally, s-ketamine pretreatment before the onset of depression prevented CUS-induced behavioral phenotypes and neuropathological changes of dorsal CA1 neurons. Our results suggest that s-ketamine reduces or prevents functional I_h from being increased following CUS, which contributes to the rapid antidepressant effects and resiliency to CUS.

Disclosures: C. Kim: None. **D. Johnston:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.14/Y3

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: R01 MH105910-04
MH093897-06A1

Title: Ketamine but not rapastinel increases mPFC pyramidal cell GCaMP fluorescence

Authors: *B. D. HARE, R. S. DUMAN;
Yale Sch. of Med., New Haven, CT

Abstract: Depression is a debilitating disorder that impacts nearly twenty percent of the population and is predicted to be a leading cause of disability worldwide in the near future. Monaminergic antidepressaants are effective in only thirty percent of cases and may take weeks to months of treatment to ease the symptoms of depression. The NMDA receptor antagonist ketamine has been shown to produce an antidepressant response within hours that persists for up to a week. Clinical and pre-clinical studies have pointed to an increase in frontal cortex activity after ketamine as a potentially important component of the mechanism underlying the antidepressant actions of ketamine. The development of genetically encoded calcium indicators (GECI; e.g. GCaMPs) allows in-vivo monitoring of fluorescence associated with calcium activity such as that produced with synaptic activity and action potential generation. Here we sought to determine the effect of rapid acting antidepressants on GCaMP fluorescence in mPFC pyramidal cells immediately following treatment. Male and female C57BL6J mice were implanted with fiber optic cannula over ventral mPFC CaMKII-expressing cells virally transfected with GCaMP6f. Animals were habituated to the fiber photometry apparatus for 30 minutes prior to treatment with saline or a rapid acting antidepressant compound and data was collected for an additional hour. We observed a clear increase of GCaMP fluorescence in the 30 minutes following ketamine administration that was dose dependent (3mg/kg, 10mg/kg, 30mg/kg, 100mg/kg; IP) indicating an increase in ventral mPFC activity immediately after treatment. Rapastinel, another rapid acting antidepressant that is a positive allosteric NMDA receptor modulator without the psychotomimetic side effects and abuse potential of ketamine was also tested. Administration of rapastinel (3mg/kg; IV) did not produce the increase in GCaMP signal that was observed with ketamine. These studies suggest that the mPFC response to rapid acting antidepressant treatment may vary with the mechanistic target, and point to the potential utility of GECIs in delineating population activity that is necessary for rapid antidepressant effects versus that associated with off target effects. Studies are ongoing to examine the effects of ketamine enantiomers and metabolites on GCaMP fluorescence.

Disclosures: B.D. Hare: None. **R.S. Duman:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.15/Y4

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH Grant MH093897
NIMH Grant MH105910
State of Connecticut

Title: Distinct projections of the medial prefrontal cortex underlie the rapid antidepressant actions of ketamine

Authors: *R. SHINOHARA, B. D. HARE, R.-J. LIU, R. S. DUMAN;
Dept. of Psychiatry, Yale Univ. Sch. of Med., New Haven, CT

Abstract: Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, triggers a rapid antidepressant response, even in patients categorized as treatment-resistant. Preclinical studies indicate that glutamatergic signaling in the medial prefrontal cortex (mPFC) is critical for the therapeutic actions of ketamine. A low-dose ketamine produces a paradoxical burst of glutamate in the mPFC and leads to increased synaptic number and function. We recently identified a key neuronal population in the mPFC that underlies the actions of ketamine; optogenetic activation of dopamine receptor D1 (*Drd1*)-expressing neurons in the mPFC reproduced the rapid and sustained antidepressant responses, and optogenetic or chemogenetic silencing of these neurons blocked the behavioral actions of systemic ketamine in the forced swim test (FST) and novelty suppressed feeding test (NSFT). Optogenetic activation of *Drd1*-expressing neurons in the mPFC increased c-Fos expression in the basolateral amygdala (BLA) and anterior portion of the bed nucleus of the stria terminalis (aBNST). Additionally, bilateral optogenetic activation of mPFC *Drd1* terminals in the BLA resulted in the rapid antidepressant responses in the FST and anxiolytic response in the NSFT 1 day after photostimulation. Although bilateral optogenetic activation of mPFC *Drd1* terminals in the aBNST resulted in no obvious response in the FST, an anxiolytic response in the NSFT was observed 1 day after photostimulation. Here we tested the necessity of these mPFC circuits in the actions of ketamine by pairing Cre-dependent AAV expressing inhibitory DREADD (hM4Di) that was infused into the mPFC with retrograde AAV expressing Cre that was infused into either BLA or aBNST. Behavioral testing was conducted 1 day after administration of a DREADD agonist clozapine-N-oxide (CNO) (1 mg/kg) and ketamine (10 mg/kg). Chemogenetic silencing of the mPFC-BLA pathway prior to ketamine dosing blocked the ketamine response in the FST but had no effect on the ketamine response in the NSFT. By contrast, chemogenetic silencing of the mPFC-aBNST pathway prior to ketamine dosing blocked the ketamine response in the NSFT and female urine sniffing test (FUST) but no effect on the ketamine response in the FST. These findings indicate that ketamine-induced plasticity of the mPFC distributes information to downstream circuit targets (i.e. BLA and aBNST) that produce distinct behavioral responses. Further experiments are being conducted to investigate whether ketamine induces neuroplasticity in the BLA and aBNST and to test the role of neuroplasticity in these regions in the action of ketamine.

Disclosures: **R. Shinohara:** None. **B.D. Hare:** None. **R. Liu:** None. **R.S. Duman:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.16/Y5

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH Grant MH093897
NIMH Grant MH105910
State of Connecticut

Title: Temporal characterization of sex-specific changes in glutamatergic/GABAergic neuron markers expression in a mouse model of stress

Authors: *C. JIANG[1], R. S. DUMAN[2];
[1]Dept. of Psychiatry, Yale Univ. Sch. of Med., New Haven, CT; [2]Dept. of Psychiatry, Yale Univ. Sch. Med., New Haven, CT

Abstract: Depression is a highly prevalent mental illness with devastating public health impact. According to the National Center for Health Statistics (NCHS), depression affects 8.1% of U.S. adult population in a given 2-week period and women are nearly twice as likely as men to develop depression. Evidence from clinical and preclinical studies indicates that stress exposure increases vulnerability to depression and depression leads to altered physiological and molecular responses to stress. Dysfunctional glutamatergic and GABAergic neurotransmission systems have been proposed to underlie the link between stress and depression. However, which system is more susceptible to stress and whether sex differences exist in this susceptibility remain incompletely understood. Our current study seeks to address these issues utilizing chronic variable stress (CVS), a stress paradigm that has been demonstrated to trigger the onset of depression-like phenotypes in a sex-specific time course, and biochemical approach to characterize the changes in the expression of various glutamatergic and GABAergic neuron makers in a temporal and sex-specific manner. We subjected 9 - 12-week-old female and male C57BL/6J mice to CVS for different lengths of time (3 days, 6 days, 12 days and 21 days) and used western blot analysis to examine the changes in the expression of AMPA receptor subunit GluR1, postsynaptic density protein 95 (PSD-95), vesicular glutamate transporter 1 (VGLUT1), vesicular GABA transporter (VGAT) and GABA-synthesizing enzyme (GAD2) in synaptosomal preparation of medial prefrontal cortex (mPFC). Our preliminary data reveals a trend of reduction in the levels of these markers in mPFC synaptosomes of both female and male mice stressed for 21 days. In addition, we observed higher expression levels of PSD-95 and GAD2 in males compared to females in the naïve control groups. Interestingly, GluR1 expression was decreased more rapidly in stressed females than males, reaching a significantly lower level at the 6-day stress timepoint compared to naïve female controls. In contrast, males manifested more

pronounced reduction in VGAT expression than females, showing a significant difference at the 6-day stress timepoint compared to naïve male controls. These preliminary results indicate that sex differences in glutamatergic/GABAergic systems potentially exist at baseline and at different stages of stress exposure. Experiments are being conducted to validate these observations in a new cohort of mice and to assess the changes in the expression of these neuronal makers in other brain regions that are implicated in the stress response and depression.

Disclosures: C. Jiang: None. **R.S. Duman:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.17/Y6

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIMH Grant MH045481
NIMH Grant MH093897
Allergan Inc., NJ, USA

Title: Initial cellular trigger for rapid antidepressant actions of rapastinel: Cell-type specific role of NMDAR and dopamine receptors

Authors: *S. POTHULA[1], T. KATO[1], R.-J. LIU[1], M. WU[1], A.-N. SLIBY[1], R. SHINOHARA[1], P. BANERJEE[2], R. DUMAN[1];
[1]Dept. of Psychiatry, Yale Univ., New Haven, CT; [2]Allergan Inc.,, New Jersey, NJ

Abstract: Rapastinel (Glyx-13) is a novel NMDA receptor (NMDAR) modulator that enhances NMDAR function. It exerts rapid antidepressant effects similar to ketamine but has a lower propensity to induce dissociative and psychotomimetic side effects than ketamine. Although, recent studies demonstrate that the actions of rapastinel require BDNF release, mTORC1 signaling, and synapse formation in the medial prefrontal cortex (mPFC), the initial cellular trigger and molecular target for rapastinel remains unknown. Here, we use a combination of AAV2-viral mediated cell specific knockdown, behavioral, pharmacological, microdialysis and electrophysiological approaches to identify the molecular target, initial cellular trigger, and neuronal cell type involved in the actions of rapastinel. The results demonstrate that knockdown (KD) of the GluN2B subunit of NMDARs on glutamatergic but not GABAergic neurons in mPFC blocks the antidepressant effects of rapastinel. In contrast, the actions of ketamine were blocked by knockdown of GluN2B on GABAergic but not glutamatergic neurons. In support of rapastinel's direct action on principal neurons, microdialysis studies demonstrate that ketamine, but not, rapastinel increases glutamate release in mPFC. Electrophysiological studies conducted in layer V pyramidal neurons in mPFC slices are consistent with these findings, demonstrating

that bath application of rapastinel causes a dose dependent increase in NMDA-induced inward current while ketamine completely blocks the NMDA response. We further examine the role of two major subtypes of mPFC principle neurons in the actions of rapastinel, and demonstrate that GluN2B KD on Drd1, but not Drd2-expressing principal neurons blocks the antidepressant-like effects of rapastinel. We also show that pharmacological inhibition of D1R but not D2Rs in the mPFC blocks the rapid antidepressant behavioral actions of rapastinel. Together, our findings demonstrate that the GluN2B subunit on glutamatergic neurons is the cellular target for rapastinel, and that rapastinel enhances NMDA-induced inward currents on these mPFC principle neurons. These findings are also consistent with in vivo microdialysis studies demonstrating that ketamine, but not rapastinel causes a rapid, transient increase in extracellular glutamate. The results also show that D1Rs are required for the rapid antidepressant actions of rapastinel. Ongoing experiments are evaluating the cell-type specific role of GluN2A and D1Rs in the antidepressant actions of rapastinel.

Disclosures: S. Pothula: None. **T. Kato:** A. Employment/Salary (full or part-time):; Sumitomo Dainippon Pharma Co., Ltd. **R. Liu:** None. **M. Wu:** None. **A. Sliby:** None. **R. Shinohara:** None. **P. Banerjee:** A. Employment/Salary (full or part-time):; Allergan Inc., New Jersey. **R. Duman:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.18/Y7

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH Grant GR038169

Title: Cell type specific transcriptome analysis in medial prefrontal cortex and ventral hippocampus after ketamine treatment

Authors: *B. LEE, M. J. GIRGENTI, M. V. FOGACA, R. S. DUMAN;
Dept. of Psychiatry, Yale Univ. Sch. Med., New Haven, CT

Abstract: Ketamine, an anaesthetic and hallucinogenic drug, has received a great deal of attention over the past decade as a rapid-acting antidepressant and recently esketamine, a form of ketamine, has been approved by the Food and Drug Administration (FDA) for depression treatment. Two hypotheses exist to explain the underlying mechanisms of ketamine as an antidepressant. One is the “disinhibition” hypothesis, which suggests that ketamine selectively blocks NMDA receptors on GABA interneurons resulting in decreased inhibitory input to pyramidal neurons. The other is the “direct” hypothesis, which suggests that ketamine blocks NMDA receptors on glutamatergic neurons resulting in homeostatic control of synaptic activity.

Therefore, transcriptional changes within different cell types in response to ketamine treatment may provide further insights of the underlying mechanisms of ketamine as an antidepressant. Given the significant volume reduction in medial prefrontal cortex (mPFC) and hippocampus in depressed patients, and studies showing the important role of ventral hippocampus in controlling depression symptoms, we decided to isolate specific cell populations from fluorescently tagged, rodent mPFC and ventral hippocampus after ketamine treatment. Although ketamine acts rapidly, evidence of the contributions of the spine formation to its sustained antidepressant effect indicates that transcriptomic changes 24 hours after treatment could provide insight into the molecular underpinnings of this effect. Using CaMKII, SST and PV subtype-specific fluorescence activated cell sorting (FACS) from transgenic mice and RNA sequencing, we identified distinct transcriptome profiles from each subtype of neuron. Pathway and network analysis suggest distinct molecules and pathways for each cell type and could explain the mechanisms underlying ketamine's antidepressant effects. We also analyzed mRNA from both male and female mice to allow for identification of gender specific transcriptome changes that could help to elucidate the neurobiology underlying the higher prevalence in women. Ultimately, these findings could lead to identification of novel biomarkers or potential therapeutic targets.

Disclosures: B. Lee: None. **M.J. Girgenti:** None. **M.V. Fogaca:** None. **R.S. Duman:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.19/Y8

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: NIH K08 MH107662
Neuroscience Fellows at the University of Michigan
Frances and Kenneth Eisenberg Scholar Award
University of Michigan Kavli Postdoctoral Enrichment Program

Title: Stress-sensitive antidepressant-like effects of ketamine in the mouse forced swim test

Authors: *P. J. FITZGERALD, J. Y. YEN, B. O. WATSON;
Psychiatry, Univ. of Michigan, Ann Arbor, MI

Abstract: Major depression is a stress-linked disease with significant morbidity worldwide. The anesthetic drug ketamine is of growing interest in depression treatment since in responsive individuals a single dose has rapidly acting (i.e., within hours) antidepressant effects that can be sustained for at least a week. This combination of fast action and a therapeutic effect that lasts far beyond the drug's half-life points to a unique mechanism of action. In this reverse translational study, we investigate how and whether the well-documented effects of ketamine in rodents are

sensitive to the stress state of the animal. Male C57BL/6J mice (n=8 per stress/drug condition) were given a single injection of vehicle (0.9% saline; i.p.), 10 mg/kg ketamine, or 30 mg/kg ketamine, and were tested in the forced swim test (FST) 24 hours and 7 days later, as well as in the open field test on the eighth day. Unstressed mice had normal group housing, environmental enrichment, and experimenter (5 days) pre-handling, whereas stressed animals were subjected to chronic mild stress, including two-week unpredictable chronic stress (UCS). Ketamine (24 hours post-injection) increased immobility and decreased swimming behavior (depression-like effects) in unstressed animals and did the opposite in UCS animals, where these opposing effects are similar to recent human findings. In summary, chronic stress interacts with ketamine to modulate its effects in the C57BL/6J mouse FST, which reinforces the relevance of this test, and this strain of mice, to human, stress-induced depression.

Disclosures: P.J. Fitzgerald: None. **J.Y. Yen:** None. **B.O. Watson:** None.

Poster

509. Depression and Bipolar Disorders: Ketamine in Animal Studies

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 509.20/Y9

Topic: G.04. Mood Disorders – Depression and Bipolar Disorders

Support: PRIN 2015HRE757_003, MIUR, Italy

Title: Ketamine modulates spontaneous and miniature excitatory synaptic currents in the medial prefrontal cortex of acutely stressed rats

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Abstract: The cellular and functional changes underlying the adaptive or maladaptive behavioral effects of an acute stressor are not well understood. In the medial prefrontal cortex (mPFC) of preclinical animal models, an acute stressor may rapidly change dendritic morphology and synaptic function. In the male rat mPFC, the foot-shock stress protocol (FS) rapidly (~1 hr) increases the number of excitatory synapses, the readily releasable Glu vesicle pool, [K^+]-evoked Glu release from synaptosomes (doi.org/10.3389/fpsyt.2015.00060), and the amplitude of spontaneous excitatory postsynaptic currents (sEPSCs) recorded in L2/3 pyramidal neurons (Pyr). Within 24 hrs, FS induces shrinkage of apical dendrites, while no information exists for sEPSCs. Miniature excitatory synaptic currents (mEPSCs) have been suggested to have a neurotrophic and homeostatic role, but the effects of FS on mEPSCs are unknown.
To understand the sustained effects of FS on Glu transmission in the mPFC and its regulation by

ketamine at antidepressant dosage, synaptic currents were recorded 24 hrs after FS in visually identified layer 2/3 Pyr of prelimbic mPFC in slices from adult male rats. Animals subjected to a 40-min session of inescapable FS (FS group), animals injected with ketamine (10mg/kg) 6 hrs after FS, and controls (CTR) were compared. The amplitude, area, rise, decay, and inter-event intervals of mEPSCs and sEPSCs were analyzed. mEPSCs in the FS group showed minor changes in frequency (small increase) and ampitude (small decrease) vs CTR. Ketamine after FS increased mEPSC frequency and peak amplitude and accelerated rise and decay with no change in area, vs CTR. The above effects were significant with the Kolmogorov-Smirnov test on pooled cumulative unbinned data but not with 2-way ANOVA of binned histograms. sEPSCs frequency in the FS group had a small decrease, with no change in waveform vs CTR. Ketamine after FS produced similar effects on sESPCs as for mEPSCs. Overall, this work indicates that, 24 hrs after FS, minor changes occur in miniature and spontaneous synaptic currents at layer 2/3 Glu synapses of the mPFC of adult male rats. Ketamine effects on Glu synaptic currents of stressed animals suggest changes in synapse morphology and/or dendritic localization.

Disclosures: F. Salerno Scarzella: None. **E. Schiavon:** None. **L. Musazzi:** None. **L. Forti:** None. **M. Popoli:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.01/Y10

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA-IRP Grant ZIADA000566

Title: Midazolam potentiates heroin-induced brain hypoxia, hypothermia, and behavioral inhibition

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Abstract: Benzodiazepines are important therapeutic drugs, but they are often abused and co-abused with opioids. Clinical evidence suggests that benzodiazepines can inhibit respiration, and when combined with the respiratory-depressive effects of opioids, may increase likelihood of death. In this study we used oxygen sensors coupled with high-speed amperometry and multi-site thermorecording to examine how intravenous (iv) midazolam, a potent benzodiazepine, modulates the brain hypoxic and temperature effects of iv heroin in freely-moving, male Long-Evans rats. Oxygen levels and brain temperature were assessed with high temporal resolution in the nucleus accumbens (NAc), and additional thermorecordings from temporal muscle and subcutaneous space allowed us to assess drug-induced changes in metabolic brain activity and

skin vascular tone. When administered alone, midazolam (2 mg/kg) modestly decreased NAc temperature but had no evident effects on NAc oxygen levels. In contrast, heroin (0.4 mg/kg) induced a strong decrease in oxygen that was followed by a weaker, rebound-like oxygen increase which appears to be caused by cerebral vasodilation and subsequent increases in cerebral blood flow (CBF). Midazolam pretreatment did not affect heroin-induced brain hypoxia but potentiated the initial hypothermia induced by heroin. In contrast, co-administration of these drugs potentiated heroin-induced oxygen decrease and brain hypothermia. This potentiated oxygen decrease appears to be caused by decreases in CBF due to strong peripheral vasodilation, thus opposing increases in CBF normally induced by heroin-alone. Midazolam co-administered with heroin thus appears to "disenable" this latter adaptive mechanism, resulting in more prolonged and sustained brain hypoxia. Co-administration of heroin and midazolam also resulted in enhanced locomotor inhibition and ataxia/loss of behavioral control, which caused some rats to collapse, resulting in nose and mouth occlusion which created a secondary hypoxic phase. Our results thus highlight the exaggerated dangers of the polydrug abuse of benzodiazepines with potent opioid drugs and they could have important implications for human drug users, as combined use not only results in sustained brain hypoxia but creates conditions of loss of motor control which could result in asphyxia and death.

Disclosures: A. Afzal: None. **E.A. Kiyatkin:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

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Program #/Poster #: 510.02/Y11

Topic: G.08. Drugs of Abuse and Addiction

Support: Grant-in-Aid for Scientific Research(C) 16K09197

Title: Effect of transporter inhibitors on brain concentration of peripherally injected diphenidine

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Abstract: Background: Diphenidine (DPD) is one of the new psychoactive substances. The chemical structure of DPD is similar to phencyclidine and ketamine. DPD and some of its derivatives are designated as controlled drugs in Japan and many other countries. The mechanisms of the drugs are common and known as the NMDA receptor antagonist. We have reported that DPD increased locomotor activity and stimulated A10 nervous system, which is known as reward system and strongly related with drug addiction, rather than A9 nervous system in rat. In this study we estimated time course of the brain concentration of DPD by using rat

brain microdialysis and evaluated the effect of several transporter inhibitors related to blood-brain barrier.
Method: Male Slc:Wistar/ST rats were anesthetized and stereotaxically implanted a microdialysis probe with a dialysis area of 2 mm length in the nucleus accumbens (NAc, A +2.0 mm, L +1.5 mm from the bregma, V -6.0 mm from the skull). On the next day, perfusion was performed in a plastic cage with free access to food and watery gel. An inhibitor was injected subcutaneously 1 hr before i.p. injection of 10 mg/kg DPD. Dialysate were collected every hour and then analyzed by LC-MS/MS. LC-MS/MS analysis was performed with an API3200 QTRAP System (Applied Biosystems) coupled to a Shimadzu HPLC LC20A system. Reversed-phase L-Column2 ODS (150 mm x 1.5 mm I.D., 5 μm) was used as the separation column. The separation was performed with 70% methanol in 10 mM ammonium formate (flow rate 0.1 ml/min). DPD was detected by ESI-positive mode. The product ion m/z 86 from m/z 235 of DPD was the most suitable ion for quantitative determination using selected reactions monitoring (SRM).
Result and discussion: DPD was detected in the dialysate from rat brain after i.p. injection. The highest concentrations were observed at 30 minutes and the concentrations were decreased time-dependent manner. This result proved that DPD pass through the blood-brain barrier. The DPD concentration in the dialysate was significantly increased by pretreatment of P-glycoprotein inhibitors such as verapamil and quinidine. And also, an organic cation transporter inhibitor, diphenhydramine, significantly increased the DPD concentration in the dialysate. However, no difference was identified between DPD levels in the blood of the inhibitors and saline pretreatment groups. The results indicated that P-glycoprotein and organic cation transporter has an important role in the transportation of DPD across the blood-brain barrier.

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Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.03/Y12

Topic: G.08. Drugs of Abuse and Addiction

Title: Changes in the structure and diversity of the rat gut microbiota induced by volatilized cocaine and adulterants

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Abstract: A close relationship between the gut microbiota (GM) and neuropsychiatric disorders has been suggested. However, only a few studies have investigated the GM in the context of drug addiction. In addition to the intranasal consumption, cocaine can be smoked (i.e., cocaine base named crack or coca-paste, CP). The consumption of CP or crack is associated with a very high abuse liability and toxicity. We have demonstrated that CP seized samples contained caffeine and phenacetin as main active adulterants, which may potentiate its motivational, reinforcing, and toxic effects. It has been recently reported that rats chronically treated with antibiotics show important changes in GM and also potentiate the sensitization process to cocaine. However, the effect of volatilized cocaine and adulterants on the GM still remains unexplored. We evaluated the effect of volatilized cocaine and two adulterants on the structure, diversity, and functionality of the GM in rats. Male adult rats were chronically exposed to the fume of cocaine, caffeine, and phenacetin during 14 days. At the end of the treatment, feces were collected and the structure, composition, and functional predictions of the gut microbiota were analyzed. Cocaine significantly decreased the community richness and diversity of the GM while both cocaine and phenacetin drastically changed its composition. Phenacetin significantly increased the Firmicutes-Bacteroidetes ratio compared to the control group. When the predicted metagenome functional content of the bacterial communities was analyzed, all the treatments induced a dramatic decrease of the aromatic amino acid decarboxylase gene, suggesting that neurochemical changes can occur. Our results show for the first time that cocaine and adulterants are able to modify the GM. Although further studies are needed, our results support that GM could be a site of action for treatment in drug addiction.

Disclosures: C. Scorza: None. **C. Piccini:** None. **M. Martinez Busi:** None. **J. Abin Carriquiry:** None. **P. Zunino:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.04/Y13

Topic: G.08. Drugs of Abuse and Addiction

Support: SAF2016-75347-R
PND-20161004
2017SGR979

Title: Role of the terminal amine group of alphaPVP derivatives (synthetic cathinones) inducing psychostimulant and rewarding effects

Authors: *R. LÓPEZ-ARNAU[1], L. DUART-CASTELLS[1], N. NADAL-GRATACÓS[2], X. BERZOSA[2], M. MURALTER[1], M. CARBÓ[3], J. CAMARASA[1], D. PUBILL[1], E. ESCUBEDO[1]; [1]Dept. of Pharmacology, Toxicology and Therapeut. Chem., Fac. of Pharm. and Food Science,

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Abstract: New psychoactive substances is a term describing analogues of classic psychostimulant abused drugs. One of the most prevalent and abused group is synthetic cathinones, whose effects are similar to amphetamine, cocaine or MDMA. Data suggest that, by analogy, other synthetic cathinones will join to the recreational drug market and most of them may have strong rewarding effects and have abuse liability. Thus, the aim of the present research was to study the role of the terminal amine group of pentiophenone derivatives (a class of synthetic cathinones) inhibiting dopamine and noradrenaline uptake as well as their psychostimulant and rewarding effects. N-ethyl-pentedrone (NEP) (1, 3 or 10 mg/kg, i.p.), α-pyrrolidinopentiophenone (α-PVP) (1, 3 or 10 mg/kg, i.p.) or N-piperidyl-pentedrone (NPP) (7.5, 25 or 75 mg/kg, i.p.) were administered to Swiss CD-1 male mice (8 weeks-old) and their locomotor activity was recorded for 60 min. Moreover, conditioned place preference experiments were also performed at the same doses. Synaptosomes from male rat (Sprague-Dawley, 200-250 g) striatum were used for [^{3}H]dopamine (DA) and [^{3}H]noradrenaline (NA) uptake experiments. NEP and α-PVP (3 and 10 mg/kg) induced a dose-dependent increase in locomotor activity while NPP produced only a slight increase in locomotion at the highest doses tested. Once again, both NEP and α-PVP produced similar place preference conditioning at the highest doses tested (3 and 10 mg/kg) although NEP also produced a significant preference score at a dose of 1 mg/kg. Therefore, and based on the ability of producing rewarding effects, NEP may have potential for abuse and addiction comparable to α-PVP. However, NPP only induced rewarding effects at the lowest dose tested (7.5 mg/kg) although the same dose did not produce an increase in the locomotor activity. On the other hand, the three substances were able to inhibit [^{3}H]DA and [^{3}H]NA uptake in rat synaptosomes. The IC_{50} values (nM) of DA and NA uptake for NEP, α-PVP and NPP were 696.4 ± 54.4 and 93.7± 0.4, 129.3 ± 7.3 and 18.8 ± 0.6, 887.9 ± 83.1 and 279.3 ± 48.8, respectively. Therefore, the order of potency inhibiting both DA and NA uptake was α-PVP> NEP≥ NPP. In conclusion, the terminal amine group of these compounds seems to impact in their potential to induce rewarding and psychostimulant effects as well as to inhibit DA and NA uptake. The present results also provide new information about the effects of new synthetic cathinones that may appear soon on the drug market.

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Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.05/Y14

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant MH040223

Title: Cue-induced reinstatement following chronic intravenous ketamine self-administration in male and female Long-Evans rats

Authors: *D. P. HAGARTY, C. STRONG, K. L. MANN, J. BREEDLOVE, K. SCHOEPFER, S. CAJUSTE, M. KABBAJ;
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Abstract: Ketamine's rapid and long-lasting antidepressant effects have shown great promise for helping Major Depressive Disorder (MDD) patients with Treatment Resistant Depression (TRD). However, ketamine itself is addictive and little has been done to examine the abuse potential of repeated exposure treatment regimens for TRD. Additionally, most current research has been done in only male subjects and primarily assessed higher doses of ketamine. Depression is twice as prevalent among women as compared to men and clinical studies suggest that women cycle through the stages of addiction at a faster rate than men. Furthermore, our lab previously demonstrated that female rats were more sensitive to ketamine's antidepressant-like and addictive-like properties, so more research is needed to examine the addictive potential between sexes. Given that men and women receive the same dose of antidepressant ketamine in clinical settings, the aim of this study was to investigate ketamine's addictive properties across a range of doses to better assess the safety of repeated ketamine treatment using a rodent model. Here, we investigated sex differences in the reinforcing properties of repeated ketamine to determine the optimal dose of ketamine for future studies examining both addiction-like behaviors and antidepressant outcomes without eliciting addictive-like behaviors. We examined ketamine's reinforcing properties by using a self-administration (SA) paradigm to assess measures of drug acquisition, maintenance, extinction, and reinstatement in male and female rats. Independent groups of rats were assigned to self-administer various doses of ketamine (0, 0.125-, 0.250-, or 0.500 mg/kg/infusion, i.v.). Male and female rats self-administered under fixed ratio 1, 3, and 5 (FR1, FR3, FR5) schedules of reinforcement during daily 2-hour long sessions. Following SA, animals were exposed to 10 days of extinction followed by cue-induced reinstatement 24-hours after the last extinction session. Preliminary data suggest sex differences in both infusions and active responding during SA, extinction, and cue-induced reinstatement, such that females consistently had more infusions and responses than males at higher doses. Future research should investigate the specific molecular mechanisms and circuitry underlying cue-induced reinstatement of ketamine SA.

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Poster

510. Psychostimulant Actions on Neural Circuits

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.06/Y15

Topic: G.08. Drugs of Abuse and Addiction

Support: FDN-154294

Title: Methamphetamine-induced behavioral sensitization: A role for brain CYP2D1

Authors: *M. R. STOCCO[1], S. MIKSYS[1,2], F. B. WADJI[1], B. ZHAO[1,2], A. EL-SHERBENI[1], R. F. TYNDALE[1,2];
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Abstract: Introduction: Brain CYP2D metabolism of methamphetamine (METH) is a potential source of variation in response, abuse liability, and neurological outcomes. CYP2D is genetically variable and metabolizes many CNS active drugs, including metabolizing METH to metabolites amphetamine (AMP) and 4-OH-METH. Brain CYP2D influences CNS drug levels and response, as has been shown in rats with opioid analgesia. Inhibiting brain CYP2D could increase brain METH and decrease metabolite levels. Increases in stereotypy, ambulation, and rearing would suggest a METH effect, while the reverse would indicate a metabolite effect. We hypothesized that METH, more so than AMP and 4-OH-METH, induces behavioral sensitization, and that inhibiting rat brain CYP2D metabolism would increase sensitization following repeated METH administration. Methods: Male Wistar rats were injected with METH (0.5 mg/kg SC) daily for 7 days and on challenge days 11 and 27. Stereotypy, ambulation, and rearing responses were assessed. Twenty hours prior to each METH injection, rats were given intracerebroventricular pretreatment injections of the CYP2D suicide inhibitor propranolol (80 µg; N=11) to irreversibly inhibit brain CYP2D, or of vehicle (20% cyclodextrin solution; N=12). Two replications were performed, each with N=5-6 rats per pretreatment group. Results: Vehicle pretreated rats exhibited modest sensitization of stereotypy, but no change in ambulation or rearing. Compared to day 1, their stereotypy time was *higher* on challenge day 27 (ANOVA main effect of session, $p<0.0001$; Bonferroni post hoc, $p<0.05$). CYP2D inhibitor pretreated rats exhibited greater sensitization. Compared to day 1, their stereotypy time was *higher* on days 4-7 and challenge days 11 and 27 (Bonferroni post hocs, all $p<0.05$); their ambulatory activity was *lower* on challenge day 27 (main effect of session, $p<0.05$; Bonferroni post hoc, $p<0.05$); and their rearing episodes were *lower* on days 5-7 and challenge days 11 and 27 (main effect of session, $p<0.01$; Bonferroni post hocs, all $p<0.05$). Comparing pretreatments, rats given CYP2D inhibitor (versus vehicle) exhibited *greater* stereotypy sensitization (main effect of pretreatment, $p<0.0001$), as well as a *decrease* in ambulatory activity (main effect of pretreatment, $p<0.0001$) and in rearing

episodes (main effect of pretreatment, $p<0.001$). Conclusions: These data indicate (1) a role for brain CYP2D in METH responses, and (2) a greater contribution of METH than of AMP and 4-OH-METH to METH sensitization. Variation in brain CYP2D metabolism is a potential novel mechanism contributing to differences in response following repeat METH exposure.

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Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.07/Y16

Topic: G.08. Drugs of Abuse and Addiction

Title: Drug addiction and withdrawal induce changes in behavior and epigenetic biomarkers

Authors: *A. ZMAROWSKI, S. REED, B. LEARN, C. BOND, J. CLAYBOURNE, R. LORDO, D. S. B. S. SILVA, R. SPURBECK;
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Abstract: Drug abuse, including prescription drug abuse, is an immense problem with huge economic and sociological costs. The present study was designed to assess behavioral and epigenetic changes after inducing drug dependence and during withdrawal using positive controls. Animals (8-9 animals/sex/group) were given subcutaneous injections once daily for 30 days with d-Amphetamine (AMPH, 0.08 or 0.1 mg/kg), Diazepam (DIAZ, 5 or 10 mg/kg) or Morphine (7.5 or 15 mg/kg). Control animals received sterile water for injection. After the last day of dosing, animals underwent a drug-free 7-day withdrawal period. Functional observational battery (FOB) assessments, including behavioral, physiological and reflex tests, were conducted by an examiner blinded to dose groups between 1-3 hours after dosing. Locomotor activity was measured for 4 hours per occasion. Behavioral testing was conducted once prior to dosing, on treatment Day 1, Day 30, and Days 1-7 of the withdrawal period. After 7 days of withdrawal, animals were euthanized and brains dissected. For morphine treated rats and controls, DNA and proteins were extracted from the hypothalamus for analysis of two epigenetic marks: DNA methylation and histone modifications. Reduced representation bisulfite sequencing was conducted to obtain DNA methylation profiles and Mod Spec® was used to measure the abundance of 80 different histone modifications to identify targets effected by morphine addiction and withdrawal. Differences in FOB endpoints and changes in locomotor activity were noted for drug treated groups primarily on Day 1 and Day 30. Most behavioral differences resolved by Day 7 of the withdrawal period. Data from the present study will contribute to the characterization of the neurobiological effects of different drug classes in addiction and

withdrawal. The epigenetic targets will enable development of new diagnostics for opioid addiction/withdrawal and provide the basis for development of alternative treatments for addicted individuals.

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Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.08/Y17

Topic: G.08. Drugs of Abuse and Addiction

Title: Effects of chronic co-administration of modafinil and citalopram on motor activity and the subsequent oral self-administration of modafinil

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Abstract: Most drugs of abuse share a common neurobiological substratum; particularly related to an increase in the release of dopamine (DA) in areas of the mesocorticolimbic circuit. There is evidence that besides norepinephrine (NE), serotonine (SER) activity seems to play an important role in addictive behavior. Cocaine, a psychostimulant with high addictive potential, acts enhancing the monoaminergic activity of DA, NE and SER. Modafinil is a week psychostimulant used for sleep disorders acting on DAT and NET but without affinity on SERT, and at the same time, no addictive potential has been described for this drug. On the basis of the differential action on monoamine activity, it is possible that the co-administration of modafinil plus citalopram (a specific inhibitor of SER reuptake) could conferring or increase the incentive value of modafinil and so facilitate its subsequent self-administration. Due to there is no background in the literature, the initial approach was to evaluate different doses of modafinil and citalopram. Seven groups of male rats 60-day old were treated chronically (16 days) with, either modafinil (MOD) in doses of 30 or 60mg/kg alone or co-administered with citalopram (CIT) at doses of 3mg/kg and 5mg/kg, 40 min before evaluating the motor activity. In addition, the behavior of anhedonia was assessed at 48, 72 and 96h after the treatment was interrupted. Oral modafinil self-administration was assessed after 12h of liquid restriction. Motor activity was diminished in 60MOD+3CIT and 60MOD+5CIT groups during the initial phase of pharmacological treatment. The co-administered groups 30MOD+3CIT and 60MOD+3CIT show high values of anhedonia, which were increasing over time in comparison with the other groups in the abstinence phase. At the same time, these groups show higher MOD self-administration than the other groups, and only the 60MOD+3CIT group showed motor activity sensitization

respect of the vehicle group. The co-administration of 30MOD+3CIT and 60MOD+3CIT seem to damp the hyperactivity effect of MOD as a psychostimulant drug; produces more signs of drug-withdrawal and an apparent proclivity to an increased consumption of modafinil.

Disclosures: E. Yepez: None. **L. Molina-Martinez:** None. **J. Juarez:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA Grant R01DA03889
NIDA Grant T32DA007209
Heffter Research Institute

Title: The effects of inhaled salvinorin A on resting state functional connectivity in humans

Authors: *M. K. DOSS, R. R. GRIFFITHS, D. G. MAY, M. W. JOHNSON, J. M. CLIFTON, F. S. BARRETT;
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Abstract: Salvinorin A is a potent κ-opioid receptor agonist and the main psychoactive constituent of *Salvia divinorum*, an atypical dissociative hallucinogen that is used recreationally and remains legal in many countries. Inhaled salvinorin A leads to a rapid onset and short duration of subjective effects that include a sense of depersonalization and derealization, as well as peculiar subjective effects that may mimic some of those of typical dissociative hallucinogens (i.e., NMDA receptor antagonists like ketamine) and classic psychedelics (i.e., 5-HT_{2A} receptor agonists like psilocybin). Additionally, some evidence suggests a rapid antidepressant effect of salvinorin A like ketamine and psilocybin, drugs with noteworthy effects on default mode network (DMN) connectivity. In a single-blind, placebo-controlled design, we conducted the first functional magnetic resonance imaging study with acute administration of inhaled salvinorin A to explore its effects on resting state functional connectivity in 12 healthy participants. Participants inhaled placebo (hot air) or vaporized salvinorin A (15 μg/kg) at the beginning of two separate 20-minute resting state scans. Participants listened to ambient music and wore eyeshades during each scan. Across the whole brain, salvinorin A (compared to placebo) decreased the number of significant static functional connections. This effect was especially robust within the DMN during the first half of the scan, and persisting attenuation of the DMN during the second half of the scan correlated with the duration of subjective drug strength. Salvinorin A was also found to decrease static connectivity within the frontoparietal network and a subcortical network that includes the salience network. An increase in functional connectivity

was found between medial and lateral visual networks during salvinorin A scans, perhaps reflecting visual distortions. Finally, analyses on functional connectivity dynamics revealed that salvinorin A reduced variability in functional connectivity within the DMN and within the medial and lateral visual networks. These findings reflect both similarity and dissimilarity with the neural effects of other hallucinogens, suggesting neural mechanisms that are unique to the altered state produced by salvinorin A.

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Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

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Program #/Poster #: 510.10/Y19

Topic: G.08. Drugs of Abuse and Addiction

Support: VIEP-BUAP 2019

Title: Acute oral administration of clobenzorex increases rectal temperature without altering motor activity in rat

Authors: *B. GÓMEZ-DE LOS SANTOS[1], D. MARCELO-PÉREZ[1], G. D. APÓSTOL-DEL ROSAL[1], A. PATRICIO-MARTÍNEZ[1,2], I. D. LIMÓN[1];
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Abstract: Clobenzorex (Clx) is an amphetamine-like widely used in morbid obesity treatments, due to it is a potent anorexigenic agent as well as being a less potent stimulant agent. Because of this drivers use the Clx to decrease the fatigue and insomnia for long periods. Acute treatment with amphetamine (AMPH) has been evidence to produce hyperthermia, decrease dopamine levels and tyrosine hydroxylase inmunoreactivity in the striatum, which has been associated with locomotor damage. The aim of this study was to evaluate the effect of acute oral administration of Clx on rectal temperature and motor activity in rats. Male Wistar rats were used, which were divided into three experimental groups: a control group (SSI, n=6), an amphetamine group (3 mg/kg, n=6) and a clobenzorex group (60 mg/kg, n=6). The administration of the drugs was carried out orally three times in an interval of three hours, in a single day. Rectal temperature was measured half an hour before starting administration begin administration and every hour after the first administration. Register ended two hours after the last administration. The following day was evaluated the motor activity in the open field model (Columbus Instrumens, Ohio USA). The results show that the acute oral administration of Clx and AMPH increases the rectal temperature two and three hours after the first administration, respect to control group.

However, no significant changes in motor activity shown. These results suggest that acute oral administration of Clx and AMPH produce hyperthermia because of the norepinephrine and glucocorticoids' release at the peripheral level. Nevertheless, in this condition do not produce change in motor activity. Support VIEP-BUAP 2019.

Disclosures: B. Gómez-De los Santos: None. **D. Marcelo-Pérez:** None. **G.D. Apóstol-del Rosal:** None. **A. Patricio-Martínez:** None. **I.D. Limón:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.11/DP11/Y20

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: G.08. Drugs of Abuse and Addiction

Support: WSU FRAP Award

Title: The effects of chronic methamphetamine on LINE-1 activity in rat striatum, hippocampus and prefrontal cortex

Authors: *A. B. MOSZCZYNSKA;
Wayne State Univ., Detroit, MI

Abstract: Methamphetamine (METH) is a widely abused psychostimulant with the potential to cause a broad range of cognitive and psychomotor deficits as well as neurobehavioral abnormalities when abused chronically, particularly at high doses. These deficits are related to METH neurotoxicity in the striatum, prefrontal cortex and hippocampus. Transposable elements are repetitive DNA sequences that can induce epigenetic alterations in the genome. Activation of transposable Long INterspersed Element 1 (LINE-1) is associated with several neurological diseases as well as with drug abuse. However, there is very limited data on the effects of high-dose METH on the activity of LINE-1 in adult brain. Employing 2-month-old male Sprague-Dawley rats, pyrosequencing, and real-time quantitative PCR, we examined a few markers of LINE-1 activity in the striatum, dentate gyrus, and prefrontal cortex of chronic METH-treated rats and saline controls. This study demonstrates that chronic administration of neurotoxic METH doses results in significantly increased expression of LINE-1-encoded ORF-1 (Open Reading Frame 1 mRNA) in rat striatum at 24h after the last dose of the drug and decreased ORF-1 expression on the 7thday of METH withdrawal, with the dentate gyrus developing tolerance to these METH effects and prefrontal cortex showing unaffected LINE-1 activity at both time points (as assessed by multiple unpaired two-tailed *t*-tests followed by the Holm-Sidak method to adjusts for the probability of Type I errors in multiple comparisons). The results

indicate that LINE-1 activation might be a new factor mediating neurotoxic effects of chronic METH in the striatum and, therefore, a new drug target against METH-induced psychomotor impairments in chronic METH users.

Disclosures: A.B. Moszczynska: None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.12/Y21

Topic: G.08. Drugs of Abuse and Addiction

Support: VIEP-BUAP-2019

Title: Chronic clobenzorex administration decreased motor behaviour without dopaminergic degeneration

Authors: *A. PATRICIO-MARTÍNEZ[1,2], G. D. APOSTOL DEL ROSAL[1], B. GÓMEZ-DE LOS SANTOS[1], F. LUNA MORALES[3], I. D. LIMÓN[1];
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Abstract: Clobenzorex is one of the five drugs most used in Mexico for the treatment of obesity. Clobenzorex´s an amphetamine-like due to the structural and stimulant similarities that they share. Several studies have shown that amphetamines induce dopaminergic neurotoxicity and neuroinflammation in the striatum, associated with motor damage. For this reason, the aim of this study was to evaluate the chronic clobenzorex administration on motor behaviour and nigrostriatal dopaminergic degeneration. Male Wistar rats were used, three experimental groups were formed: control group (n= 8) administered with SSI, amphetamine group (2 mg / kg) (n= 8) and the clobenzorex group (30 mg / kg) (n= 8), all groups were administered orally, every 24 hours, for 31 days. Every 10 days the rats were evaluated motor activity in the open field test and motor coordination in the beam-walking test. Thirty-two days post-lesion were euthanasia performed on animals to extract the brains and assess the tyrosine hydroxylase (TH), even to explore the neurodegeneration in striatum and *substance nigra pars compacta* (SNpc), by the amino-cupric silver stain. The results show that the amphetamine and clobenzorex administration decrease motor activity and increased errors number in the beam-walking test compared to the control group. On the other hand, we not found significant changes in the immunoreactivity for TH and the neurodegeneration in striatum and SNpc. These results suggest that chronic administration of clobenzorex could decrease motor function similar to amphetamine through neuroadaptive and non-neurotoxic changes in the striatum under this administration paradigm.

Disclosures: **A. Patricio-Martínez:** None. **G.D. Apostol del Rosal:** None. **B. Gómez-De los Santos:** None. **F. Luna Morales:** None. **I.D. Limón:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.13/Y22

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA024705

Title: The effects of voluntary methamphetamine vapor exposure and binge intoxication in adult Wistar rats

Authors: *A. GUTIERREZ[1,2], J. D. NGUYEN[1,2], M. A. TAFFE[1,2];
[1]Psychiatry, Univ. of California San Diego, La Jolla, CA; [2]Neurosci., The Scripps Res. Inst., La Jolla, CA

Abstract: Long-term changes in neuronal signaling and cognitive function result from chronic methamphetamine (MA) abuse. Inhalation is a major route of administration among individuals that abuse MA, yet few pre-clinical studies have examined the effects of inhaled MA. The purpose of this study was to examine the effects of MA vapor inhalation using an electronic cigarette style drug delivery system. The first experiment was designed to examine MA vapor self-administration. Adult female Wistar rats were trained to nose-poke for MA vapor at a fixed drug concentration in the vapor vehicle. Drug concentrations were then substituted across days, and concentration-response assessed. Results of this experiment confirmed modest concentration-dependent responding. The second set of experiments used a binge-like dosing regimen to determine whether repeated exposure to a high concentration of MA vapor produced effects characteristic of those produced by repeated MA injection in prior studies, e.g., neurotoxicity and cognitive deficits. For these experiments, animals were implanted with radiotelemetry devices to assess body temperature and locomotor activity during MA inhalation. Rats underwent three sessions of 30-minute MA vapor exposure, each session separated by a two-hour interval. Brain tissue was collected in one group of animals two weeks after MA dosing. A second group of animals underwent behavioral testing to examine effects of MA vapor on impulsivity in a delayed-discounting task, also starting two weeks after MA inhalation. Tissue was collected from these animals upon completion of behavioral testing. This experiment showed that binge MA exposure by vapor inhalation resulted in elevated locomotor activity and in ambient temperature-dependent changes in body temperature, characteristic of binge MA treatment by injection. Results from the delayed discounting task found MA-induced changes in impulsivity since MA-treated animals preferred a small immediate reward over a larger, delayed reward at the longest delay interval examined. Tissue analyses will provide further information

on the effects MA vapor on tissue monoamine content. The findings reported here validate a method of studying both reinforcement of MA by inhalation and cognitive effects resulting from binge MA vapor intoxication.

Disclosures: A. Gutierrez: None. **J.D. Nguyen:** None. **M.A. Taffe:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.14/Y23

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA R01DA020140

Title: Characterization of repeated exposure to ketamine and its metabolite in zebrafish larvae

Authors: *N. N. JACKSON, K. S. JONES;
Pharmacol. Dept., Univ. of Michigan Med. Sch., Ann Arbor, MI

Abstract: Ketamine is a commonly used anesthetic that blocks the ion channel pore of the N-methyl-d-aspartate receptor (NMDAR). Therapeutic interest in NMDAR pore blockers has grown considerably because it can rapidly alleviate symptoms of depression (Zaraet et al., 2006). However, the therapeutic use of ketamine is risky because it can also cause serious side effects like psychotomimesis (Domino, 1992) and repeated exposure can be habit-forming. Sensitization and tolerance are neuroadaptive processes that respectively increase and decreases drug effects during repeated exposure to drugs of abuse. Repeated exposure to ketamine has been shown to cause sensitization to the hyperlocomotor actions of ketamine, but the mechanism is unclear. Zebrafish (*Danio rerio)* is an emerging animal model in drug abuse research whose behavioral response to ketamine and other NMDAR antagonists is highly homologous to mammals. Here we examined how repeated exposure to anesthetic and sub-anesthetic doses of ketamine influences the psychomotor and anesthetic actions of ketamine. Additionally, we examined the effect of repeated exposure to ketamine's neuroactive metabolite hydroxynorketamine (6HNK). We also examined how repeated exposure to ketamine and 6-HNK impact brain-wide neuronal activity in zebrafish larvae. The current experiments were designed to examine the impact of daily exposure to ketamine or 6HNK for 5 days after 24 hpf, when zebrafish are expressing NMDARs. Drug treatment was discontinued on day 6. On day 7, larvae received an acute challenge of respective drug and behavioral data was collected. Groups of fish were fixed and stained for pERK. Preliminary data suggests the IC_{50} for ketamine in zebrafish larvae is 0.139 mM.
This study suggests chronic exposure to ketamine shows sensitization or tolerance of zebrafish locomotor activity. These experiments will potentially lead to a better understanding of the

actions of ketamine and the active metabolite 6HNK and its actions in the brain. Furthermore, these findings may contribute to the development of pharmaceutical treatments of disorders involving NMDA receptor inhibition.

Disclosures: **N.N. Jackson:** None. **K.S. Jones:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.15/Y24

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant DA R01 027222

Title: The prefrontal cortex and the caudate nucleus respond conjointly to methylphenidate (Ritalin). Concomitant behavioral and neuronal recording study

Authors: *S. S. VENKATARAMAN[1], C. CLAUSSEN[2], C. REYES-VAZQUEZ[3], N. KHARAS[2], N. DAFNY[2];
[1]Neurobio. and Anat., Wake Forest Univ. Sch. of Med., Houston, TX; [2]Neurobio. and Anat., The Univ. of Texas McGovern Med. Sch. at Houston, Houston, TX; [3]Dept. De Fisiología, Mexico, D.F., Mexico

Abstract: Methylphenidate (MPD) is the most commonly prescribed psychostimulant used in children and adolescents to treat attention deficit hyperactivity disorder (ADHD). Though MPD effectively treats the disorder in patients who are diagnosed with ADHD, it is being abused for its ability to improve cognitive enhancement and for recreational purposes. Thus, there are growing concerns regarding its addictive potential. Further, some use MPD for daily cognitive enhancement (chronic), while others use it just prior to an exam or important task (acute).Additionally, the dose of MPD abused varies from individual to individual with some abusing low dose MPD (0.6mg/kg and 2.5mg/kg) and others abusing high dose MPD (10.0mg/kg). The prefrontal cortex (PFC) and caudate nucleus (CN) are two of the brain areas that are dysfunctional in ADHD and are also involved in the reward pathway. The PFC, in particular, is involved with higher cortical processing, decision-making, impulse control and other features inhibited by ADHD. The PFC makes extensive connections with the CN. These frontostriatal connections play critical roles in procedural learning and inhibitory control.The goals of this study are to investigate acute and chronic, dose-dependent MPD exposure on behavioral activity and the PFC and CN neuronal populations in ordinary, (as opposed to ADHD or hyperactive) freely behaving adult animals implanted previously with electrodes within the PFC and CN. For this experiment, four groups of animals were used: saline (control), 0.6, 2.5, and 10.0 mg/kg MPD. It was observed that the same dose of either: 0.6, 2.5, or 10.0 mg/kg

repetitive (chronic) MPD exposure elicited behavioral sensitization in some animals and behavioral tolerance in others. Moreover, it was demonstrated that the majority of PFC units and CN units responded to MPD in a similar, dose-dependent fashion. The majority of animals expressing behavioral sensitization responded to MPD by increasing their neuronal firing rate, whereas the majority of PFC neurons recorded from animals expressing behavioral tolerance responded to MPD by decreasing their neuronal firing rate. We propose that chronic MPD exposure leads to an increase in the number of post-synaptic D1 dopamine receptors in behaviorally sensitized animals and an increase in the number of post-synaptic D2 dopamine receptors in behaviorally tolerant animals. Further, we suggest that as the PFC and CN fire together and behave similarly upon MPD exposure, they likely wire together, supporting the hypothesis that MPD use and abuse may strengthen these frontostriatal connections, which possibly underlie MPD addiction.

Disclosures: S.S. Venkataraman: None. **C. Claussen:** None. **C. Reyes-Vazquez:** None. **N. Kharas:** None. **N. Dafny:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.16/Y25

Topic: G.08. Drugs of Abuse and Addiction

Support: Taif University Grant

Title: Effects of quercetin pre-treatments and repeated toxic-dose methamphetamine on hyperthermia

Authors: *A. ALMALKI[1], Y. ALTHOBAITI[2];
[1]Dept. of Pharmaceut. Chem., [2]Pharmacol. and Toxicology, Taif Univ., Taif, Saudi Arabia

Abstract: Methamphetamine (METH) is considered one of the abused psychostimulants that has been proven to induce nerve damage due to its neurotoxic effects. High dose of METH was discovered to induce hyperthermia which has been suggested to induce neuronal damage. Finding treatment that can prevent or alleviate hyperthermia in METH abusers is critical. Many reports indicated that oxidative stress has been linked to METH induced hyperthermia. Therefore, we proposed that quercetin, well known antioxidant, can reduce the METH induced hyperthermia. Saline (1ml/kg, i.p. every 2h × 4) or quercetin (200 mg/kg i.p. every 2 hours x 4) were given at 30 min pretreatment paradigm. METH (5 mg/kg i.p. every 2 hours x 4) or Saline (1ml/kg, i.p. every 2h × 4) were given as posttreatment paradigm. Four groups of rats were used in this study; (1) saline-saline group (SS) group, (2) Saline-METH (SM), (3) Quercetin-saline (QS) group, and (4) Quercetin-METH (QM) group. Temperature was recorded at 4 time points

(0, 90, 120, and 220 mins). Temperature was elevated significantly in SM group as compared to control group at 90, 120, and 220 min. Interestingly, quercetin pretreatment was revealed to alleviate METH induced hyperthermia as compared to saline pretreatment at 120 and 220 min. This effect could be attributed to antioxidant effect of quercetin. As conclusion, quercetin could be an effective treatment in METH induced hyperthermia and neurotoxicity.

Disclosures: A. Almalki: None. **Y. Althobaiti:** None.

Poster

510. Psychostimulant Actions on Neural Circuits

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 510.17/Y26

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH DA036012

Title: Using nanoparticles to reduce methamphetamine toxicity

Authors: M. SEVERSON[1], P. JAMPANI[2], Z. WANG[2], *L. M. MCFADDEN[1];
[1]Div. of Basic Biomed. Sci., [2]Dept. of Chem., Univ. of South Dakota, Vermillion, SD

Abstract: Methamphetamine (METH) is a highly addictive psychostimulant with potentially deadly consequences. The neurotoxic effects of METH are due in part to the excessive release of dopamine (DA), serotonin (5HT) and other biogenic amines which may lead to persistent damage to DA and 5HT neurons. Currently, no pharmacological treatments for METH abuse/ overdose exist. Metal-organic supercontainers (MOSCs) are a new class of nanoscale particles featuring diverse nanoporous structures. These structures have tunable features that can be manipulated to allow specific molecules to bind to them. It is hypothesized that MOSCs may provide therapeutic potential in reducing METH-toxicity by binding transmitters released by METH, leading to a mitigation of the long-term effects. Ultraviolet-visible spectroscopy (UV-vis) was used to demonstrate that MOSCs has a binding affinity to DA and 5HT. Further, in exploratory studies, male Sprague-Dawley rats (300-400 grams) were used to assess MOSCs therapeutic potential in reducing METH-induced toxicity. Males were utilized given that previous studies have demonstrated that they have greater METH-induced toxicity compared to females. Our initial findings indicate that following a neurotoxic exposure to METH, rats had higher DA content in the MOSC infused striatum when compared to the vehicle control infused striatum, indicating the ability of MOSCs to attenuate of the neurotoxic consequences of METH (6 animals utilized in two experiments). Follow up studies to assess MOSC distribution and viability *in vivo* will also be performed. Systemic administration will also be utilized to assess MOSCs ability to cross the blood-brain barrier. Overall, these findings suggest that MOSCs may provide therapeutic potential in reducing toxicity caused by METH.

Disclosures: **M. Severson:** None. **P. Jampani:** None. **Z. Wang:** None. **L.M. McFadden:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.01/Y27

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant T32 GM-07229
P01 AG 031862

Title: Identification of a novel metabolic-epigenetic interaction network mediating learning-related histone acetylation in the brain

Authors: *D. C. ALEXANDER[1], M. MENDOZA[1], G. EGERVARI[1], P. MEWS[2], B. A. GARCIA[1], S. BERGER[1];
[1]Perelman Sch. of Med., Univ. of Pennsylvania, Philadelphia, PA; [2]Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Histone acetylation is an epigenetic activator of many types of learning and memory, including the establishment and maintenance of addiction memory. During memory formation, histone acetylation spikes at the promoters of immediate early genes, which are critical regulators of synaptic plasticity. In neurons, a metabolic protein, Acetyl-CoA synthetase 2 (ACSS2), plays an essential role in activity-dependent gene activation by converting acetate to acetyl-coA directly at the regulatory elements of induced genes. While the level of circulating acetate in the mammalian bloodstream is normally low, the consumption and subsequent metabolism of ethanol increases plasma acetate levels 20-fold. Interestingly, this alcohol-derived acetate is directly incorporated into brain histone acetylation in an ACSS2-dependent manner, providing an additional mechanism for the establishment of alcohol use disorder. This finding is striking, but many aspects of ACSS2's action on neuronal chromatin are unknown, including both its method of recruitment and its interacting partners at the chromatin. To establish ACSS2's interacting partners at the chromatin in an unbiased manner, we immunoprecipitated endogenous ACSS2 from nuclear lysate derived from C57Bl6 adult cortex and identified interacting proteins by nano liquid chromatography-tandem mass spectrometry (nLC-MS/MS). To remove non-specific interactors, we compared these results to identical IPs performed in age-matched $ACSS2^{KO}$ mice we generated by CRISPR-Cas9 on a C57Bl6 background. From these data, we described a high-confidence interactome for nuclear ACSS2, demonstrating that it interacts with known chromatin regulators and chromatin remodeling proteins. To map ACSS2's interacting partners to specific genomic loci, we performed chromatin immunoprecipitation of select factors and compared these results to ACSS2's enrichment across the genome. Finally, we

compared ACSS2's binding occupancy to RNA expression at baseline and in the context of memory formation. All molecular experiments were performed in age-matched adult mice (female and male; n=3-5 per group), and controlled for time-of-day effects. Our findings delineate the molecular components of a novel metabolic-epigenetic regulatory machine that is required for learning-related histone acetylation. In the context of alcohol use, this machinery regulates the incorporation of exogenous acetate into histone acetylation in the brain. By clarifying the protein interactome of ACSS2 in vivo, we further establish this enzyme as an important biochemical contributor to learning and memory in physiological and pathological contexts.

Disclosures: D.C. Alexander: None. **M. Mendoza:** None. **G. Egervari:** None. **P. Mews:** None. **B.A. Garcia:** None. **S. Berger:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.02/Y28

Topic: G.08. Drugs of Abuse and Addiction

Support: NARSAD Young Investigator Award (NMG)
NIDA Drug Supply Program

Title: A novel method to study prolonged reward-context associations

Authors: *G. MCKENDRICK, N. GRAZIANE;
Anesthesiol. & Perioperative Med., Pennsylvania State Univ., Hershey, PA

Abstract: Animal models have significantly contributed to the understanding of reward-related behaviors, such as in Substance Use Disorder (SUD) research. Two of the most prominent paradigms to date are operant intravenous drug self-administration (SA) and conditioned place preference (CPP), each of which have distinct advantages and disadvantages. The classic SA model benefits from voluntary drug-taking, yet it is time-consuming, often invasive, and can involve non-translational learning procedures. Traditional CPP models are valued for their emphasis on contexts, ease and quickness of use, and sensitivity to drug effects, however it is non-contingent in nature, as the experimenter controls drug exposure. Our new model integrates these two classical methods by utilizing individual benefits and simultaneously diminishing prior downsides. We used a traditional 3-compartment CPP apparatus, where each chamber differs by both visual and tactile contexts. We reformed the apparatus by adding a new plexiglass top that allows for insertion of a 10 mL drinking bottle into each of the main chambers. The bottles, made of modified serological pipettes with a stainless-steel sipper tube, allow for oral self-administration of drug-containing solutions in a specific context. Wild type C57BL/6J mice

underwent 3 habituation trials to quantify baseline preference. Drug (Sucrose (10% w/v) or Morphine (25 mg/L)) and Water were assigned to the least- and most-preferred side, respectively. Two overnight training sessions were followed by 5 conditioning days (40-60 min sessions, 2x per day), restricted to either chamber with access to respective solutions. Solution consumption was recorded in mL. The next day mice were given open access to all chambers (Preference 1d test), and time in each chamber was recorded. After 21 days of homecage abstinence, mice had another test (Preference 21d test) to examine prolonged retention of preference. We have established a novel technique to assess preference for contexts associated with rewarding stimuli, which accentuates both voluntary drug-taking and environmental conditions. The described model can be further utilized to examine alternative drugs of abuse, apply extinction training or other learning models, or allow for inclusion of neurobiological manipulations.

Disclosures: G. McKendrick: None. **N. Graziane:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.03/Y29

Topic: G.08. Drugs of Abuse and Addiction

Support: Grass Foundation
National Institute of General Medical Sciences of the National Institutes of Health under linked Award Numbers RL5GM118969, TL4GM118971, and UL1GM118970

Title: Modeling drug reward in invertebrates

Authors: A. ROMERO[1], J. F. GOMEZ-MOLINA[2], ***U. M. RICOY**[1];
[1]Dept. of Biology, Chem. and Envrn. Sci., Northern New Mexico Col., Espanola, NM; [2]Intl. Group of Neurosci. (IGN), Medellin, Colombia

Abstract: Conditioned place preference (CPP) continues to be one of the most popular models to study the motivational effects of drugs and non-drug treatments in experimental animals. With the underlying mechanisms strongly conserved in evolution, invertebrates have recently emerged as a powerful new model in addiction research. Indeed, as early as 1990, Huber et al. reported cockroaches as good candidates for neurobiology with relevant applications in biomedical research. Cockroaches represent an excellent model organism for a variety of biological and biomedical studies, including development, behavior, and neural responses. Because we can study behavioral mechanisms in cockroaches, we can study neuromodulation in a variety of different experimental paradigms. Early cockroach work focused on octopamine (OA) and

serotonin response in the nervous system. OA is a neuromodulator, neurotransmitter and neurohormone in insect nervous systems prompting the organism for "dynamic action." We use two species of cockroach (Periplaneta Americana and Blaptica Discoidalis). A total of 20 cockroaches, 10 of each species, were placed one at a time in a single lane of a Plexiglas apparatus with vanilla and peppermint. Each session was recorded from a top and side view for three minutes; video sessions were analyzed at a later time for the amount of time spent on each compartment X of the apparatus (X= Intermediate, Vanilla, or Peppermint). Our results show a strong Vanilla preference and peppermint avoidance for both South American and North American roaches. We also examined grooming behavior and found Vanilla to increase exploration and grooming whereas Peppermint had little effect on behavior. In a separate experiment, we show how OA alone increases exploratory behavior and neural excitability of the giant interneurons in the North American cockroach. The neuropil of the thoracic ganglia contains many catecholamine-histofluorescent processes bearing varicosities, providing a possible anatomical substrate for dopamine release sites. It is proposed that release of these biogenic amines may contribute to the modulation of the cockroach place preference behavior. Collectively, these findings suggest that the cockroach model is a useful approach to examine basic mechanistic questions in drug addiction.

Disclosures: **A. Romero:** None. **J.F. Gomez-Molina:** None. **U.M. Ricoy:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.04/Y30

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA IRP / NIH

Title: *In vivo* labeling and molecular characterization of active neurons in the infralimbic cortex using a genetically encoded photo-activatable calcium integrator (CaMPARI2)

Authors: *R. MADANGOPAL[1], S. J. WEBER[1], V. LENNON[1], L. E. KOMER[1], F. RUBIO[1], V. MENON[2], E. R. SCHREITER[3], B. T. HOPE[1];
[1]Natl. Inst. on Drug Abuse IRP, Baltimore, MD; [2]Dept. of Neurol., Columbia Univ., New York, NY; [3]Howard Hughes Med. Institute, Janelia Farm Res. Campus, Ashburn, VA

Abstract: Animals learn to associate cues (e.g. lights or tones) with rewards (e.g. food or cocaine). These learned associations are thought to be encoded by specific patterns of sparsely distributed neurons called '*neuronal ensembles*' that are selectively activated by these stimuli. Our lab and others have used the immediate early gene Fos to identify neuronal ensembles in rodent models of reward-related behaviors and have shown that they mediate these learned

behaviors. However, Fos protein expression is too slow to distinguish the active neuron patterns underlying individual stimulus-reward associations during these tasks.
To address this problem, we developed a technique to permanently label active neurons *in vivo* during ongoing behavior with sub-second resolution using an activity-dependent photoconvertible protein named CaMPARI2 (calcium-modulated photo-activatable ratiometric integrator). Using UV light, CaMPARI2 can be rapidly and permanently converted from its native green state to an 'active' red state only in neurons with strong activation (high intracellular calcium) time-locked to light delivery.In this study, we used CaMPARI to identify unique molecular alterations within activated neurons in the infralimbic cortex (IL) of rats during cocaine relapse. We first injected a virus to express CaMPARI2 in the infralimbic cortex, implanted optical fibers for UV light delivery and installed intravenous catheters for drug delivery. We then trained these rats to self-administer cocaine (3 h/d x 14 d, FR1, 0.75 mg/kg/inf) followed by 21 days of abstinence. On test day, we used UV light to permanently label IL neurons activated during the first minute of cue-induced drug-seeking. The control group received the same training and abstinence experience but active neurons were labelled during 1 minute of novel context exposure; based on past experience, we expect that the neurons labelled here will be distinct from the relapse-activated ensemble.
We are currently using fluorescence activated cell sorting (FACS) to isolate the active (red-labeled) neurons and will validate the expression of immediate early genes in active cells from both groups. We will also asess molecular alterations in the active neuron populations of the relapse and novel context groups. This is part of our overall strategy to identify the engram underlying maladaptive memories in addiction.

Disclosures: R. Madangopal: None. **S.J. Weber:** None. **V. Lennon:** None. **L.E. Komer:** None. **F. Rubio:** None. **V. Menon:** None. **E.R. Schreiter:** None. **B.T. Hope:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.05/Y31

Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA IRP/ NIH
PRAT 1FI2GM117583-01
NIDA K99 DA045662-01

Title: The iDISCO-SMART pipeline for whole brain activity mapping following incubation of palatable food seeking

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Abstract: We have been using the neuronal activity marker Fos to identify neuronal ensembles that mediate reward seeking and relapse. Here, we optimized the iDISCO+ immunolabeling procedure and developed an open source R package called SMART (Semi-Manual Alignment to Reference Templates) to map Fos-positive ensemble neurons across whole mouse brains. SMART extends the Wholebrain analysis framework by streamlining brain-to-atlas registration, simplifying registration correction, and accounting for non-uniform morphing along the anterior-posterior axis during iDISCO+. We used iDISCO-SMART to map brain-wide activity following incubation of food reward craving.
Methods: We trained CD-1 mice to self-administer palatable food pellets and then tested them for relapse to food seeking after 1,15, or 60 homecage abstinence days. We perfused and extracted their brains 90 min after the relapse tests and labeled 'active' Fos-positive nuclei across the brain. We then imaged Fos-immunofluorescence using light-sheet microscopy and used SMART to map "incubation-associated" neural activity patterns across the whole brain.
Results: The mice showed time-dependent increases in food seeking (non-reinforced lever presses in the presence of the food-associated cues) after homecage abstinence, with peak responding after 60 days (incubation of food craving). Currently, we are using SMART to analyze the Fos-expression data and identify the brain-wide neural correlates of incubation of food craving.
Conclusions: At the meeting, we will present data on the functional connectome underlying incubation of palatable food seeking and introduce SMART, an open-source analytical R-package for whole brain activity mapping using volumetric light sheet fluorescence microscope datasets.

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Poster

511. Drugs of Abuse: Learning and Memory II

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MH114990

DA042514
DA041778
DA000467

Title: A dopamine-induced coordinated gene expression program regulates neuronal function and cocaine response

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Abstract: Drugs of abuse increase dopamine concentrations in the nucleus accumbens, a key reward structure that integrates contextual and cue-related information and regulates motivated behavior. This surge of dopamine triggers cell signaling cascades that converge in the nucleus to cause changes in gene expression, which are thought to lead to the observed functional and structural alterations in the reward circuit after exposure to drugs of abuse. Here, we defined a dopamine-regulated gene expression program in cultured striatal neurons and engineered a large-scale multiplexed CRISPR activation strategy to recreate this program. Induction of dopamine-responsive genes generated a secondary synapse-centric transcriptional wave, altered striatal physiological properties *in vitro*, and enhanced cocaine sensitization *in vivo*. These results provide proof of principle evidence that activity-dependent gene programs are sufficient to initiate both physiological and behavioral adaptations. Ongoing work aims to examine and manipulate the transcriptional dynamics of neuronal ensembles, a sparse population of cells activated during learning and reactivation of the associated memory, which are defined by the activity-dependent expression of *Fos*. Fos-expressing ensembles in different brain areas have recently been shown to mediate a number of drug-related behaviors, which implies that transcriptional processes within this small number of sparse neurons could be important for encoding and maintaining associative memories.

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Poster

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Title: Social reward learning in adolescent mice using conditioned place preference

Authors: *C. P. CANN, C. N. MILLER, R. MARINO, M. VENNIRO, B. T. HOPE, L. R. WHITAKER;
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Abstract: Social interaction promotes survival by helping animals to form stable and supportive social groups. Additionally, maladaptive social behavior is a hallmark of disorders such as autism and schizophrenia. In many different animal species including humans, social interaction under the right circumstances can be inherently rewarding. Despite its importance, very little is known about the neurobiological substrates that mediate social reward learning. To study the rewarding properties of social interaction, we used a social conditioned place preference (CPP) procedure. We discovered that mice form a significant preference for the social interaction-paired context, spending an average of 230 seconds longer in the paired context after social conditioning. This was only expressed during the adolescent period (P21-P49), in agreement with previous studies. Learned associations between natural rewards, including social interaction, and environmental stimuli are capable of driving goal-directed behavior. These associations are thought to be encoded by functional alterations within neuronal ensembles, or specific patterns of neurons activated by reward-predictive stimuli. Fos, an immediate early gene, can be used to identify strongly activated neurons within ensembles. We used Fos immunohistochemistry to determine which brain regions play a critical role in learning about social rewards. We identified several key brain regions that are strongly active when exposed to the social-paired environment. Our future goal is to characterize and manipulate social reward ensembles to uncover the neurobioloical substrates of social associative learning.
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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIDA IRP / NIH

Title: Neurobiological substrates of discriminative stimulus controlled incubation of cocaine craving

Authors: *V. A. LENNON, S. J. WEBER, L. E. KOMER, R. MADANGOPAL, L. R. WHITAKER, B. J. TUNSTALL, J. M. BOSSERT, Y. SHAHAM, B. T. HOPE;
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Abstract: Animal models of incubation of drug craving have primarily focused on the role of conditioned stimuli (CSs) signaling drug delivery. In a recent study we trained rats to self administer cocaine (or palatable food pellets) under the control of discriminative stimuli (DSs). We then tested them for reward during abstinence and demonstrated incubation of DS controlled cocaine seeking (but not food seeking) in the absence of drug paired CSs for up to 300 days of abstinence. Here, we identify neurobiological substrates underlying this DS controlled incubation.
Using Fos as a marker for recent neuronal activity, we found that several brain regions, including the prelimbic and infralimbic subregions of the prefrontal cortex, had increased activity following cocaine seeking during a relapse test after 21 days of abstinence (relative to no test controls). We then used microinjections of a GABA receptor agonist cocktail (0.3 nmol/side baclofen, 0.03 nmol/side muscimol) to suppress activity in these regions and found that injections into the infralimbic cortex reduced DS controlled drug seeking during the day 21 relapse test session but not DS controlled drug taking during training. In contrast, microinjections of the selective D1 receptor antagonist SCH39166 (1ug/side) into either the prelimbic or infralimbic cortex had no effect during either DS controlled cocaine taking or cocaine seeking.
Our data suggest that incubation of DS controlled drug seeking is mediated in part by infralimbic cortex in a D1 independent manner. We are currently assessing the role of other brain regions identified by our Fos study in this new form of incubation.

Disclosures: V.A. Lennon: None. **S.J. Weber:** None. **L.E. Komer:** None. **R. Madangopal:** None. **L.R. Whitaker:** None. **B.J. Tunstall:** None. **J.M. Bossert:** None. **Y. Shaham:** None. **B.T. Hope:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

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Program #/Poster #: 511.09/Y35

Topic: G.08. Drugs of Abuse and Addiction

Title: Alcohol derived acetate promotes brain histone acetylation and alcohol related learning

Authors: *G. EGERVARI[1], P. MEWS[2], R. NATIVIO[1], S. SIDOLI[1], G. DONAHUE[1], S. I. LOMBROSO[1], D. C. ALEXANDER[1], S. L. RIESCHE[1], E. A. HELLER[1], E. J. NESTLER[2], B. A. GARCIA[1], S. L. BERGER[1];

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Abstract: Ethanol binds to various receptors in the brain. It is, however, often overlooked that alcohol metabolites, primarily acetate, also reach and affect the brain. In neurons, histone acetylation and gene expression are dependent on the metabolite acetyl-CoA that is produced from acetate by chromatin-bound ACSS2. Strikingly, using in vivo stable isotope labeling in mice, we found that acetate derived from alcohol metabolism is readily incorporated into brain histone acetylation in an ACSS2-dependent manner. Here, we explore the functional relevance of this novel pathway. We used an array of in vitro and in vivo molecular (LC-MS/MS, RNAseq, ChIPseq) and behavioral (ethanol conditioned place preference) experiments to study the importance of alcohol-derived acetyl group deposition. The contribution of ACSS2 was assessed in ACSS2 KO mice as well as by viral-mediated knock-down of ACSS2 in the dorsal hippocampus. Molecular experiments were performed in three or more biological replicates per group. Behavioral experiments were performed using 10-12 replicates/group, and included both male and female mice of 8-10 weeks of age. Behavioral experiments were scored by two independent and blinded investigators. State of the art statistical methods were applied to ensure scientific rigor and reproducibility. We found that exposure to alcohol and its metabolite acetate led to rapid and transient histone acetylation in the brain in an ACSS2-dependent manner. Using heavy labeled stable isotopes, we showed that this is in part mediated by direct incorporation of injected or alcohol-derived acetate. Furthermore, injection of labeled alcohol into a pregnant mouse resulted in incorporation of labeled acetyl groups into gestating fetal brains, indicating that the acetate passes through the placenta and might play a role in fetal alcohol syndrome. In isolated primary hippocampal neurons, extracellular acetate induced learning and memory-related transcriptional programs that were sensitive to ACSS2 inhibition. In addition, we found that alcohol induces histone acetylation (H3K9ac, H3K27ac ChIPseq) in an ACSS2-dependent manner in vivo, inducing genes implicated in neuronal function, learning, memory and alcohol use. Strikingly, we found that ACSS2-mediated histone acetylation is required for the encoding of alcohol-related environmental cues in vivo. Our findings establish a novel and direct link between alcohol metabolism and ACSS2-dependent histone acetylation in the brain.Importantly, we show that this metabolic-epigenetic pathway plays a critical role in encoding alcohol-associated memories, which drive craving and relapse in human alcohol users.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA019526

Title: Altered actin filament dynamics in the *Drosophila* mushroom bodies lead to fast acquisition of alcohol consumption preference

Authors: *A. BUTTS[1], S. OJELADE[3], A. RODAN[1], A. ROTHENFLUH[2];
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Abstract: Alcohol use is highly prevalent in the United States and across the world, and every year millions of people suffer from alcohol use disorders (AUDs). While the genetic contribution to developing AUDs is estimated to be 50-60%, many of the underlying molecular mechanisms remain unclear. Previous studies from our lab revealed that *Drosophila* lacking RhoGAP18B and Ras Suppressor 1 (Rsu1) display reduced sensitivity to ethanol-induced sedation. Both Rsu1 and RhoGAP18B are negative regulators of the small Rho-family GTPase, Rac1, a modulator of actin dynamics. Here we investigate the role of Rac1 and its downstream target, the actin-severing protein cofilin, in alcohol consumption preference. We show that these two regulators of action dynamics can alter experience-dependent alcohol preference in a bidirectional manner: expressing either activated Rac1 or dominant-negative cofilin in the mushroom bodies (MB) abolishes experience-dependent alcohol preference. Conversely, dominant-negative Rac1 or activated cofilin MB expression lead to faster acquisition of alcohol preference. Our data show that Rac1 and cofilin activity are key to determining the rate of acquisition of alcohol preference, revealing a critical role of actin-dynamics regulation in the development of voluntary self-administration in male *Drosophila*.

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Poster

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NIH R25 NS080687

Title: The molecular mechanisms of ethanol neuroadaptation

Authors: *A. ANQUEIRA[1], A. GHEZZI[2];
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Abstract: Alcohol consumption is known to induce cognitive impairments mainly affecting executive functions, episodic memory, and other capacities related to brain function. Nevertheless, the cellular and molecular mechanisms underlying such interactions is still unknown. Recent evidence has uncovered a similar interaction between ethanol exposure and cognitive function in the fruit fly, Drosophila melanogaster, which opens the way for molecular studies in a genetically tractable model system. Using an olfactory conditioning assay where an odorant is used as a conditioned stimulus (CS) and is paired with a heat shock used as an unconditioned stimulus (US), it was shown that Drosophila larvae can learn to avoid the odor in future exposures. However, when the animals are exposed to a short acute dose of alcohol, they are no longer able to learn this association. Interestingly, larvae that have undergone prolonged chronic ethanol exposure seem to successfully avoid the odorant paired with the heat shock just as well as control ethanol-naive larvae, which is suggestive of ethanol-induced neuroadaptations. Our aim is to understand the genetic and cellular components responsible for this adaptation. For this, we employ RNA Sequencing technology to evaluate differences in gene expression in the brain of larvae chronically exposed to ethanol and in control larvae. With the knowledge obtained from this study we could be able to understand ethanol's effect on learning and memory and gain an insight into how addiction may be contributing to damages in this behavior.

Disclosures: A. Anqueira: None. **A. Ghezzi:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

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Program #/Poster #: 511.12/Y38

Topic: G.08. Drugs of Abuse and Addiction

Title: Sex-differences in ethanol conditioned place preference in mice

Authors: *P. KOZAN, E. ALVARADO, P. D. RIVERA;
Dept. of Biol., Hope Col., Holland, MI

Abstract: Addiction is a compulsive behavior that affects ~275 million people worldwide (World Health Organization). Previous studies show the importance of sex-differences in describing pathologies of mental health disorders, such as addiction, between males and females. Moreover, the difference in immunity and inflammatory responses between males and females implicate the impact of sex hormones, namely estrogen, on immune responses in both humans and mice. Research has shown that receptors for estrogen (ERs) and estradiol, a specific type of estrogen produced in the ovaries, play a significant role in the modulation of innate immune cells and thereby innate immune responses. However, little is known about the influence of sex hormones on innate immune system during the process of addiction. One way to determine the innate immune involvement is to focus on microglia, resident immune cells found in the brain,

and their function during the onset of addiction. First, a group of mice were introduced to ethanol conditioned place preference (eCPP). In a parallel group of mice, levels of testosterone and estrogen and presence of Fos were examined in males and females at 4 distinct points during a 3 week eCPP behavioral paradigm. Mice were sacrificed 90 minutes after eCPP pairing, test, week 1 extinction, and week 3 extinction. Next, immunohistochemistry (IHC) was used to examine microglia and Fos (Iba1+) in mice brains of males and females in ethanol treated mice compared to water controls. Blood samples were also analyzed to determine levels of estrogen and testosterone. Finally, the original group of mice was sacrificed and presence of testosterone, estrogen, and Fos were examined. A comparison of sex hormones and rewarding behavior was assessed in a sex-dependent manner. If we can understand the contribution of resident microglia and sex hormones to the onset of addiction in a sex-dependent manner, we may be able to develop sex-specific treatments of addiction. Future experiments will replicate this process using other drugs of abuse, such as morphine.

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Poster

511. Drugs of Abuse: Learning and Memory II

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Support: Mitsubishi Tanabe Pharma Research Agreement

Title: A longitudinal fMRI resting-state study of reward-circuit plasticity induced by chronic ethanol exposure in rats

Authors: M. ESGUERRA[1], H. M. WIESNER[2], C. E. HUTCHISON[1], W. ZHU[2], Y. ZHANG[2], A. K. ZILVERSTAND[3], J. ZIMMERMANN[1], W. CHEN[2], X. H. ZHU[2], ***M. J. THOMAS**[1]; [1]Neurosci., [2]Radiology, [3]Psychiatry, Univ. of Minnesota, Minneapolis, MN

Abstract: A wealth of neuroimaging research in humans has demonstrated aberrant resting-state brain function after chronic alcohol use. However, it is difficult from these studies to distinguish abnormalities that may pre-date alcohol abuse from those induced by alcohol experience. To address this gap, we collected functional magnetic resonance imaging resting-state data (rs-fMRI) in 10-12 week-old female Wistar rats prior to (t1) and at the end (t2) of 7 weeks of intermittent ethanol vapor (12h on:12h off; target range 150-250 mg/dL); at the start (t3) and end (t4) of the 3-week withdrawal; and after a yohimbine injection (t5, same session as t4)—a model of stress-induced relapse. To characterize changes in rs-fMRI directly induced by chronic alcohol exposure and withdrawal in this translational model, we used the analytical methods employed in human resting-state studies of chronic alcohol abuse. Neuroimaging was performed

at 16.4T (t1-t4) and 9.4T (t4-t5). Rats were anesthetized with 1% isoflurane via inhalation, and vital signs were monitored throughout (~2.5h sessions). As each rat habituated to the scanner, we constructed structural/anatomical brain images using T2-weighted fast-spin-echo mapping sequences. For rs-fMRI analyses, following standard preprocessing, images were co-registered to a down-sized rat brain atlas. Preliminary network analysis of changes in reward circuits revealed that the relative size of nucleus accumbens (NAc)-linked networks decreased from the start (t1) until end (t2) of ethanol exposure, and partially recovered from the start (t3) until the end (t4) of withdrawal. The pharmacological stress challenge (t5) reversed this effect, renewing the reduction in relative size. Similar to the NAc network, hippocampal- and amygdala-connected networks decreased following chronic ethanol (from t1-t2), but in contrast to the NAc network, these two networks did not recover between the start until the end of withdrawal (from t3-t4). Similar to the NAc network, hippocampal- and amygdala connected networks were reduced in size during the pharmacological stress challenge (t5). Our findings establish that chronic ethanol exposure produces widespread, but not uniform, changes in reward circuit dynamics in the mammalian brain. The changes identified here are persistent—far outlasting the period of ethanol exposure itself. Furthermore, stress exposure during late withdrawal exacerbated the decreases in connectivity between specific nodes in reward circuits (NAc and BNST). These data outline specific aspects of neural plasticity that may provide fruitful targets for new therapeutic interventions for those suffering from AUD.

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Poster

511. Drugs of Abuse: Learning and Memory II

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Title: Ventral paired median neurons mediate state-dependent alcohol memory

Authors: *K. M. NUNEZ[1], M. TALAY[2], G. BARNEA[2], K. R. KAUN[2];
[1]Mol. Pharmacol. and Physiol., [2]Neurosci., Brown Univ., Providence, RI

Abstract: Alcohol is a widely abused drug, that imposes substantial social, economic, and global health burdens. Despite recent advances, the neural and molecular mechanisms through which alcohol affects the brain, and the underlying reward circuitry, is poorly understood. Moreover, a changing external and internal environment further complicates factors by shifting the internal state of an animal. However, it is not well understood how an animal's internal state can influence reward processing and alcohol memory circuitry. We sought to investigate the neural substrates necessary for state-dependent alcohol reward memory in *Drosophila melanogaster* by focusing on how food-deprivation influences acquisition and expression of memory for alcohol-associated cues. We found a role for a discrete subset of octopamine neurons specifically in food-deprived flies during both alcohol memory acquisition and retrieval. Tyramine-beta-hydroxylase mutants that lack the enzyme needed to synthesize octopamine, displayed a loss in memory expression in food-deprived animals. These results provide a circuit-specific mechanism through which stressors can modulate reward circuitry, thereby influencing acquisition and expression of alcohol-associated memories. As octopamine is most similar to vertebrate norepinephrine, a monoamine neurotransmitter that is involved in a diverse set of behaviors, physiological processes, we believe our results will inform the function of similar circuit motifs in vertebrate models of memory and alcohol use disorder.

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Poster

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Support: NIH grant: R01AA024526

Title: The effect of adolescent delta-9-tetrahydrocannabinol and ethanol exposure on prefrontal cortex reliant behaviors

Authors: *C. E. SMILEY, K. E. NIMCHUK, H. K. SALEH, A. M. MOORE, J. T. MCGONIGAL, J. T. GASS;
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Abstract: Cannabis is the most commonly used illicit drug with rates of use that have steadily increased over the last decade especially in the adolescent population. Chronic abuse can lead to cannabis use disorder (CUD) which has high comorbidity rates with alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD). Abuse of both cannabis and alcohol is occurring during a period of ongoing development in the prefrontal cortex which makes the adolescent brain especially vulnerable to insults from drugs of abuse. This set of studies tested the long term effects of adolescent exposure to THC and ethanol on prefrontal cortex reliant behaviors. Three separate experiments were completed to address different cognitive domains. The first experiment tested susceptibility to stress following THC and ethanol exposure. Animals were exposed to THC vapor and subsequently exposed to chronic intermittent ethanol vapor. Then, fear conditioning was tested with a series of tone-shock pairings to measure the rate at which animals acquired this learned association. Once conditioning was established, animals were tested for extinction learning to see how well they could learn new associations between previously conditioned stimuli. A second set of studies investigated the ability of adolescent THC exposure to alter ethanol seeking behavior. Animals were given five days of THC exposure followed by self-administration training to measure the levels of alcohol seeking and consumption. Once self-administration behavior was established, extinction sessions proceeded where animals were exposed to conditioned ethanol associated cues without the delivery of ethanol to see how long it took for ethanol seeking behavior to be extinguished. A third set of experiments examined the effect of THC and ethanol exposure during adolescence on cognitive flexibility. Animals were put into set-shifting training to establish lever pressing behavior before being tested in a between-session set-shift that measures behavioral flexibly. Preliminary studies have found that when adolescent animals are exposed to a combination of THC and ethanol they are more susceptible to fear conditioning and are resistant to extinction learning. THC exposed animals also showed escalated ethanol seeking in self-administration paradigms. In behavioral testing, THC and ethanol exposed animals showed a deficit in behavioral flexibility when tested in a model of strategy set shifting. These results indicate that adolescent exposure to THC and ethanol is detrimental to cognitive functioning in adulthood. Further studies are being done to elucidate the brain mechanisms that contribute to these behavioral results.

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Poster

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Topic: G.08. Drugs of Abuse and Addiction

Title: Long-term behavioral effects of nicotine and ethanol exposure in aged rodents

Authors: L. M. FOLTS, *G. M. FERNANDEZ;
St. Mary's Col. of Maryland, St. Mary's City, MD

Abstract: Co-morbid rates of alcohol and nicotine use are rising, especially given the increasing popularity of electronic nicotine delivery systems. Previous literature suggests that drug exposure during later developmental stages can have detrimental effects on learning and memory, as well as emotional regulation. Our current study examines the behavioral effects of nicotine and ethanol exposure in aged rats on spatial memory. Male and female Sprague Dawley rats, post-natal day 80, were exposed to either a subcutaneous injection of 0.4 mg/kg nicotine, intraoral gastric gavage of 20% ethanol at a dose of 4 g/kg, combined nicotine plus ethanol, or combined saline injections and water gavage. All rats received a total of 16 exposures on an intermittent, 3 day on/ 2 day off schedule. Nicotine, ethanol, and combined nicotine plus ethanol group differences were not found in Object-In- Place performance. However, when nicotine, ethanol and combined nicotine plus ethanol groups were collapsed, there was an overall effect of drug exposure on recognition memory. The drug exposed animals spent significantly more time with the displaced objects compared to saline/water controls and non- manipulated animals. There were no sex differences regardless of experimental drug grouping. Our results indicate a potential facilitation of memory as a result of drug exposure during adulthood in later senescence. Upcoming studies will also examine anxiety- like and reward seeking behavior.

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Poster

511. Drugs of Abuse: Learning and Memory II

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Detroit Wayne Mental Health Authority

Title: The role of baseline anxiety in associative learning and response to acute stress

Authors: *T. E. H. MOSES[1], E. A. WOODCOCK[2], M. K. GREENWALD[1];
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Abstract: Introduction: Acute stress impacts multiple behaviors, including learning and memory. Associative learning is the ability to remember relationships between unrelated items (e.g. object and spatial location). Acute stress impacts associative learning, but the direction of this relationship is not clearly understood. One factor that modulates acute stress-reactivity is baseline psychological state. Studies examining 2 primary stress hormones (cortisol, norepinephrine) show that biobehavioral responses to acute stress differ between patient populations. This study explores how baseline anxiety (State-Trait Anxiety Inventory [STAI]) impacts learning during acute pharmacological stress. Methods: 12 regular heroin users were enrolled in a buprenorphine-maintenance, inpatient study. Participants completed a double-blind 3x3 (9-session), placebo-controlled, randomized crossover study comparing oral dose-combinations of yohimbine (YOH 0, 27, 54mg) and hydrocortisone (CORT 0, 20, 40mg). In each dosing condition (4.5 hr post-YOH), participants completed 8 epochs of a computerized associative learning task. Learning rate (k) was modeled using a negatively accelerated function fit to block-wise performance data for each subject. Results: ANCOVA (covarying STAI scores) identified an interaction of anxiety and YOH on total recall accuracy across all 8 epochs ($F(2,20)=11.72$, $p<.001$, $\eta^2=.54$) and learning rate ($F(2,18)=3.93$, $p=.038$, $\eta^2=.30$). In the placebo condition, higher-anxious individuals had higher mean recall accuracy than those with lower anxiety. During YOH exposure, individuals with low anxiety increased their mean recall accuracy to the level of the high-anxiety group (whose learning accuracy and rate was insensitive to YOH dose). There was no significant interaction between CORT dose and anxiety. Discussion: Baseline anxiety levels impact associative learning during acute stress. Levels of norepinephrine play a role in associative learning, but these results suggest a more complex interaction. These findings suggest increased levels of norepinephrine may be advantageous in certain domains.

Disclosures: T.E.H. Moses: None. **E.A. Woodcock:** None. **M.K. Greenwald:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.18/Y44

Topic: G.08. Drugs of Abuse and Addiction

Support: NIH R01-DA009411-17

Title: Stress and drugs of abuse alter GABAergic transmission in the ventral tegmental area via chloride cotransporter KCC2 downregulation

Authors: *A. OSTROUMOV[1], B. A. KIMMEY[1], J. A. DANI[2];
[2]Dept. of Neurosci., [1]Univ. of Pennsylvania, Philadelphia, PA

Abstract: Stress and drugs of abuse trigger or modulate multiple forms of synaptic plasticity within the dopamine (DA) system, leading to maladaptive behaviors. Although glutamatergic synaptic plasticity is most commonly studied, there is a growing appreciation that inhibitory synapses also undergo plasticity and regulate circuit function and adaptability. Our findings indicate that exposure to acute stress or nicotine downregulates neuron-specific anion transporter, KCC2, leading to a depolarized $GABA_A$ reversal potential in ventral tegmental area (VTA) GABA neurons. The depolarized $GABA_A$ reversal potential results in a decreased synaptic inhibition or even paradoxical GABAergic excitation of GABA neurons. Compromised inhibition alters DA signaling in the VTA and the nucleus accumbens, linking synaptic plasticity to circuit-wide modifications. At the behavioral level, decreased KCC2 function and excitatory GABA signaling in the VTA mediate increased stress or nicotine-induced ethanol self-administration. Our most recent, unpublished data demonstrate that acute, *in vivo* injections of cocaine, morphine, and ethanol converge onto the GABAergic circuitry of the VTA. Like stress, these addictive drugs trigger KCC2-dependent depolarizing shift in the $GABA_A$ reversal potential in VTA GABA neurons. In summary, our studies demonstrate that exposure to stress or drugs of abuse trigger a currently understudied form of GABAergic synaptic plasticity in the mesolimbic circuitry.

Disclosures: A. Ostroumov: None. **B.A. Kimmey:** None. **J.A. Dani:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.19/Z1

Topic: G.08. Drugs of Abuse and Addiction

Support: CIC UMSNH 26.10
CIC UMSNH 30.2
CIC UMSNH 2.36

Title: Chronic toluene exposure produces learning and memory impairment in rats

Authors: *M. Y. GAUTHEREAU-TORRES[1], A. JACOBO-JACOBO[1], J. I. SANDOVAL-MEDINA[2], L. F. ORTEGA-VARELA[3], D. GODINEZ-HERNANDEZ[4];
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Abstract: Toluene is the most commonly misused solvent and it can be found as part of multiple products such as thinner, adhesives, gasoline, and cleaning products. The abuse of this solvent is considered a public health problem, mainly between children and adolescents. It has been documented that the deliberate use of toluene impacts on multiple systems in the body and the central nervous system (CNS) is more susceptible to the effects of the solvent. Among the actions on the CNS, cognitive damage, memory impairment and learning deficit can be mentioned; however, the evidence in literature is controversial. Currently, toluene mechanism of action is not completely known, but *in vitro* studies showed that toluene non-competitively inhibits the NMDA receptor (NMDAr), and it is believed that this receptor contributes to many of the effects caused by toluene, since NMDAr plays an important role in the processes of learning and memory. Nevertheless, the mechanism of action by which toluene can produce memory and learning alterations is not clear. The purpose of the present study was to investigate the effect of chronic toluene exposure on learning and long-term memory in rats. Male Wistar rats (200-300 g) were exposed to toluene (6000 ppm) or to air (control) during 30 minutes, twice a day, 4 weeks, in a static exposure chamber. 24 h after the end of exposures, the autoshaping learning task was performed in the conditioning chamber (Skinner box) and novel object recognition test was carried out; in addition, locomotor activity tests were made. The results showed that toluene exposure produced an increase in the number of days needed to learn the task and a decrease in the number of conditioned responses in Skinner box test; on the other hand, a loss of long-term declarative memory in the novel object recognition test was observed. In addition, toluene exposure had no effect on locomotor activity. Taken together, our results suggest that chronic toluene exposure produces impairment in learning and memory in rats; however, additional studies are needed to elucidate the mechanisms involved in these effects.

Disclosures: M.Y. Gauthereau-Torres: None. **A. Jacobo-Jacobo:** None. **J.I. Sandoval-Medina:** None. **L.F. Ortega-Varela:** None. **D. Godinez-Hernandez:** None.

Poster

511. Drugs of Abuse: Learning and Memory II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 511.20/Z2

Topic: G.08. Drugs of Abuse and Addiction

Support: George '51 and Marjorie '44 Chandler Senior Experience Fund

Title: Repeated exposure to high dose dextromethorphan impairs memory and alters c-Fos expression in adolescent male rats

Authors: E. CARLONI, J. DE CHABOT, J. BOEHLKE, C. HICKS, *L. RAMOS;
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Abstract: Dextromethorphan (DXM) is a semisynthetic derivative of morphine that acts as a N-methyl-D-aspartate (NMDA) receptor antagonist. It has potent antitussive properties and is the active ingredient in several over-the-counter cough and cold medicines (e.g. Robitussin and NyQuil). Over the last decade, DXM-containing formulations have been abused in conjunction with alcohol, particularly by adolescents, for their psychedelic and out-of-body dissociative effects (colloquially referred to as “robotripping”). Despite numerous anecdotal reports of severe adverse side-effects following high doses of DXM, there is a lack of research examining the neurobiological and behavioral effects of the drug. Therefore, the aim of this study was to investigate the neuronal and behavioral effects of repeated exposure to DXM in rats. Adolescent male Sprague-Dawley rats were administered saline, a 3.5% ethanol vehicle, or one of three doses of DXM (5, 20 or 50 mg/kg) dissolved in 3.5% ethanol. Drugs were administered by intraperitoneal injection during 3 weekend “binges” that consisted of two consecutive days of twice daily injections (separated by 1 h) followed by a 5-day washout period. One week following the last binge, rats underwent a battery of behavioral tests to determine drug-induced changes in social behavior, memory and depression-like behavior. At the end of behavioral testing, rats were challenged with their respective drug treatment and assessed for locomotor activity. Brains and plasma were collected and processed for c-Fos immunoreactivity and corticosterone levels, respectively. Somewhat surprisingly, our results showed no significant effects of DXM on social preference or depression-like behavior. However, rats repeatedly exposed to the highest dose of DXM (50 mg/kg) had significantly impaired memory on both the novel object recognition and novel object location tests. These rats also exhibited significant locomotor hyperactivity in response to a challenge injection of DXM, and reduced corticosterone levels. Examination of regional c-Fos expression showed that repeated administration of DXM significantly altered neuronal activation in several brain regions. The current findings demonstrate that repeated exposure to high doses of DXM can produce memory impairments and regional changes in brain activation, which may be related to deficits in NMDA receptor function.

Disclosures: E. Carloni: None. **J. de Chabot:** None. **J. Boehlke:** None. **C. Hicks:** None. **L. Ramos:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.01/Z3

Topic: H.01. Animal Cognition and Behavior

Title: Sex differences in meta-learning in a dynamic bandit task in mice

Authors: *C. S. CHEN[1], B. A. EBITZ[2], S. R. BINDAS[3], N. M. GRISSOM[4];
[1]Psychology, [2]Neurosci., [4]Dept. of Psychology, [3]Univ. of Minnesota, Minneapolis, MN

Abstract: There are substantial differences in the risk for multiple neuropsychiatric disorders across genders. Gender and sex differences in most performance outcome in behavioral and cognitive testings are small, but there is substantial neural evidence for sex differences in the mechanisms that are implicated in executive function and reward. This raises the possibility that disease vulnerability and resilience is conferred by differences in the cognitive strategies and neural circuits that are preferentially employed across sexes in solving behavioral tasks. Indeed, we have previously observed that female mice show modestly accelerated reinforcement learning in a test of decision making, the two-armed visual bandit task. Critically, we were able to identify strongly divergent strategies in the use of spatial versus visual information by males and females. However, how strategy selection is affected by history of choices and reward separately and how this differs between sexes both remain unclear. One hypothesis is the fundamental difference in the dynamics of reinforcement learning between sexes. To test this, we examined thirty-two 129/b6j F1 mice (16 male and 16 female) in a restless spatial two-arm bandit task that allowed us to examine reward as a dynamically changing system. The reward probabilities of two arms changed independently and stochastically over trials so that the animals could only infer values through constant sampling and integration of reward history. The result suggested similar baseline performance between sexes in the percentage of choosing the correct choice in blocks of 300 trials, but males tended to switch after wins more frequently than females. Fitting reinforcement learning models revealed that the reward prediction error (RPE) updating rate of females was higher than males overall and, unexpectedly, increased over time, indicating that females "learned to learn" faster. These results suggest that the differences in reinforcement learning and strategy selection between females and males may lie in their ability to meta-learn. This is consistent with our findings in the visual bandit task that females used a more systematic approach to learn, employing a global strategy.

Disclosures: C.S. Chen: None. **B.A. Ebitz:** None. **S.R. Bindas:** None. **N.M. Grissom:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.02/Z4

Topic: H.02. Human Cognition and Behavior

Support: PSI2016 80056-P from the Ministerio de Economía y Competitividad (MINECO) of Spain.

Title: Multifocal transcranial direct current stimulation over the left dorsolateral prefrontal cortex and left ventrolateral prefrontal cortex reduced risk-taking behavior depending on personality traits

Authors: *D. REDOLAR-RIPOLL[1], O. MARTIN DE LA TORRE[2], A. CUEVAS-GONZÁLEZ[3], D. GALLARDO-PUJOL[2];
[1]Hlth. Sci., Open Univ. of Catalonia (UOC), Barcelona, Spain; [2]Individual Diferences, Univ. de Barcelona (UB), Barcelona, Spain; [3]Biomed. Sci., Univ. Autònoma de Barcelona (UAB), Barcelona, Spain

Abstract: Background: Transcranial direct current stimulation (tDCS) with right anodal and left cathodal dorsolateral prefrontal cortex (DLPFC) montage has shown to reduce risk-taking behavior. Further evidence show that the activity in left ventrolateral prefrontal cortex (VLPFC) during uncertain reward expectancy is associated with risky decision-making. The aim of this experiment was to investigate the effect of multifocal transcranial direct current stimulation (MtDCS) over the left DLPFC and VLPFC separately on risk-taking behavior during Balloon Analogue Risk Task (BART) and the Bomb Risk Elicitation Task (BRET), taking into account individual differences in personality measured through the Big Five and the Dirty Dozen inventories. We hypothesized that cathodal MtDCS over the left DLPFC and left VLPFC would modify risk propensity according to previous studies. We also hypothesized that individual differences will have an effect on how stimulation affects risk-decision making.Methods: A mixed design was used to test for differences between independent groups (Personality and Stimulation intensity) whilst participants (34 healthy volunteers) were subjected to repeated measures (Stimulation location). The order within conditions was counterbalance [DLPFC (F3 cathodal, AF3, FC1, FC3, FC5, F5, return), VLPFC (F7 cathodal, FP1, F3, FC5, FT7, F9, return) and sham]. MtDCS (1.5 mA or 2 mA, randomly assigned) was applied for 20 minutes: 10 min before starting the BART and BRET and 10 during task performance. Personality data was collected a priori.Results: Via a latent profile analysis (LPA) we obtained three personality profiles: profile 1 (n=9) tended to be more narcissistic and Machiavellian, profile 2 (n=18) showed an average type and profile 3 (n=7) who tended to be introverts. There were no differences in pumps and parcels collected due to MtDCS intensity. During BART in the sham condition,profile 1 participants were more impulsive and showed higher pump values. When the stimulation was applied over VLPFC, profile 3 participants showed a cumulative impulsive trend. In BRET, the total parcels recollected decreased when the stimulation was applied over DLPFC for participants from profiles 2 and 3. Conclusions: These results show that MtDCS over the left DLPFC and VLPFC reduced risk-taking behavior. In addition, personality traits may have had a modulating effect on how non-invasive brain stimulation affects risk-taking decision.

Disclosures: D. Redolar-Ripoll: None. **O. Martin de la Torre:** None. **A. Cuevas-González:** None. **D. Gallardo-Pujol:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.03/Z5

Topic: H.02. Human Cognition and Behavior

Support: NIH R21 DA040773
NIH R01 DA026457
NIH T32 MH103213
NIH UL1 TR001108

Title: Neural correlates of risk and reward evidence accumulation during decision-making

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[1]Psychological & Brian Sci., Indiana Univ., Bloomington, IN; [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Several brain regions have been implicated in the evaluation of prospective outcomes during risky decision-making. However, the role of evidence accumulation indexed by attention to potential rewards with accompanying risk remains underexplored. Existing theories purport that the anterior insula (AI) and anterior cingulate cortex (ACC) are sensitive to risk, driving risk avoidance, yet other theories posit that the ACC drives approach or foraging behaviors despite potential risk. The current experiment aimed to explore these theories and discern how attention to potential rewards and penalties (i.e. lesser reward, null outcome, or loss) corresponds with activation in brain regions associated with value-based decisions.
During concurrent fMRI scanning and eye-tracking, 18 subjects were presented with a 2AFC decision between a sure-win reward or a 50/50 gamble consisting of a larger reward or penalty. Options were displayed for 7s while foveations on the prospective GambleWin, GamblePenalty, and SureWin amounts were recorded. Subjects then chose between the sure-win and gamble. For imaging analyses, individual boxcar regressors separately modeled distinct foveations of the three prospects, and data were analyzed using a GLM with random effects.
Behaviorally, within-trial preference for the gamble option was predicted by GambleReward foveations relative to GamblePenalty, and combined foveations to GambleReward and GamblePenalty, relative to SureWin. However across trials, only total time spent foveating GambleWin and GambleLoss relative to SureWin predicted a greater percentage of gambles chosen. Imaging results showed effects consistent with some regions of posterior dorsal ACC accumulating evidence in favor of the chosen option, as greater activation when subjects foveated the GambleWin was associated with choosing the gamble option. Other regions of mid-dorsal ACC apparently signaled after-the-fact that a riskier choice is likely to be made, as choosing the gamble was associated with more activation when subjects foveated the

GamblePenalty. This is consistent with a suggested ACC role in performance monitoring. Results in the AI also showed effects consistent with accumulating evidence in favor of avoiding risk, as greater activation while foveating the GamblePenalty was observed on trails when the SureWin was chosen.

Disclosures: **J. Purcell:** None. **A. Jahn:** None. **J.W. Brown:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.04/Z6

Topic: H.02. Human Cognition and Behavior

Title: Neural dynamics of value-based action selection: Effect of reward and risk on alpha and beta oscillation

Authors: *X. CHEN, Y. KWAK;
Univ. of Massachusetts, Amherst, Amherst, MA

Abstract: Neural oscillations in alpha (8-14 Hz) and beta (15-30 Hz) frequency bands are known to reflect active states of cortical processing related with motor planning and selection. The current study investigated the contribution of the alpha and beta oscillations during value-based action selection based on the associated reward and risk level. Forty-one healthy participants (17 males, 20.68 $\pm$ 1.97 yrs) performed a direction judgement task, while EEG was continuously recorded. They were asked to judge the direction of the stimulus by pressing the left or right button with left or right hand. Prior to the target stimulus, a cue which consists of the rewards associated with the two responses and the probability of the left vs. right stimulus (probability left vs. probability right: 25% vs. 75%, 50% vs. 50%, 75% vs. 25%) is presented (trial information period). The left and right responses are always assigned different magnitudes of reward (6 vs. 120). Faster and accurate responses gave larger proportion of the assigned rewards, whereas incorrect responses led to losing of the total rewards at stake. We compared the magnitude of beta and alpha oscillations during the trial information period across different cue conditions in brain regions involved in motor planning and execution, including SMA (Cz and Fcz), bilateral premotor (left: FC3, FC5; right: FC4, FC6) and M1 (left: C3, C5, CP3, CP5; right: C4, C6, CP4, CP6). We found a significant reward by probability interaction in alpha oscillations from the premotor regions. Alpha power was greater in the contralateral hemisphere assigned with lower than higher reward when the probability favored the response associated with higher reward. However, alpha power was greater in the contralateral hemisphere assigned with higher than lower reward in 50% vs. 50% probability assignment and when the probability favored the response associated with lower reward. No such pattern was found in M1. For SMA, in which no laterality is defined, we compared the neural oscillations across the three cue conditions which

differed in conflict levels. Conflict level was low when the reward and probability assignments both favored one side over the other, and high when the reward and probability assignments favored different sides. We found a main effect of conflict in alpha and beta oscillations with opposite patterns. The beta oscillations decreased while the alpha oscillations increased as the conflict level decreased.Taken together, our data suggests involvement of higher-level motor planning regions, but not the primary sensorimotor regions, in integrating reward and probability information during value-based action selection.

Disclosures: X. Chen: None. **Y. Kwak:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.05/Z7

Topic: H.02. Human Cognition and Behavior

Support: Catalyst Miami, Non-profit organization

Title: Neural correlates of risky decision-making and relations with risk- and reward-related behavior among individuals with low SES

Authors: *R. POUDEL[1], M. J. TOBIA[2], M. C. RIEDEL[2], T. SALO[1], J. S. FLANNERY[1], L. D. HILL-BOWEN[1], A. R. LAIRD[2], A. S. DICK[1], C. M. PARRA[3], M. T. SUTHERLAND[1]; [1]Psychology, [2]Physics, [3]Information Systems and Bussiness Analytics, Florida Intl. Univ., Miami, FL

Abstract: Brain activation during risky decision-making has been associated with aspects of self-reported risk- and reward-related personality metrics. However, the associations between risk-related brain activity, personality traits, and real-world behaviors remains poorly understood. To identify neural correlates of risky decision-making we employed a variant of the Balloon Analogue Risk Task (BART) and collected fMRI data from individuals (*n*=27) with low SES (income<$19,000/yr). To characterize relationships with personality traits and real-world financial behavior, participants also completed self-report surveys assessing aspects of risk (Attitude Towards Risk: ATR) and reward sensitivity (Behavioral Approach System: BAS) and participated in a financial savings program where their saving behaviors were tracked over a 6-month period. We expected differential activation in reward-related regions during BART and expected such activation to correlate with ATR scores, BAS scores, and financial saving outcomes. Regarding BART task effects, we observed increased activity during the decision-making phase of the task in the left medial frontal gyrus, bilateral thalamus, right putamen, and bilateral insula (Fig. 1). Furthermore, right thalamus activity was negatively correlated with ATR and BAS scores and left insula activity was negatively correlated with BAS scores (Fig. 2). This

indicated that lower activity in the right thalamus was associated with higher risk attitudes and reward sensitivity, and lower activity in the left insula was associated with higher reward sensitivity. Importantly, saving outcomes were negatively correlated with frequency of explosion, a metric of risk-taking behavior during the BART (Fig. 3). This indicated that more frequent balloon explosions were related to lower savings outcomes. Overall, these findings provide insight into the neural correlates of risky decision-making and their relationship with risk-related personality measures and demonstrate an association between laboratory and real-world behaviors.

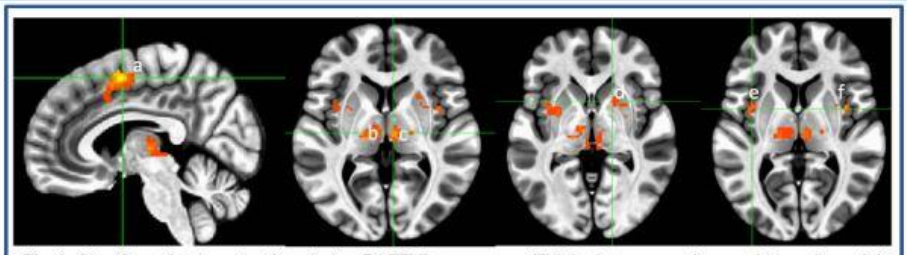

Fig 1. Significant brain activation during BART Pump versus Think phase was observed in regions: (a) medial frontal gyrus, (b) left thalamus, (c) right thalamus, (d) right putamen, (e) left insula and (f) right insula (clusters represent activation during Pump > Think; $P_{corrected} < 0.01$).

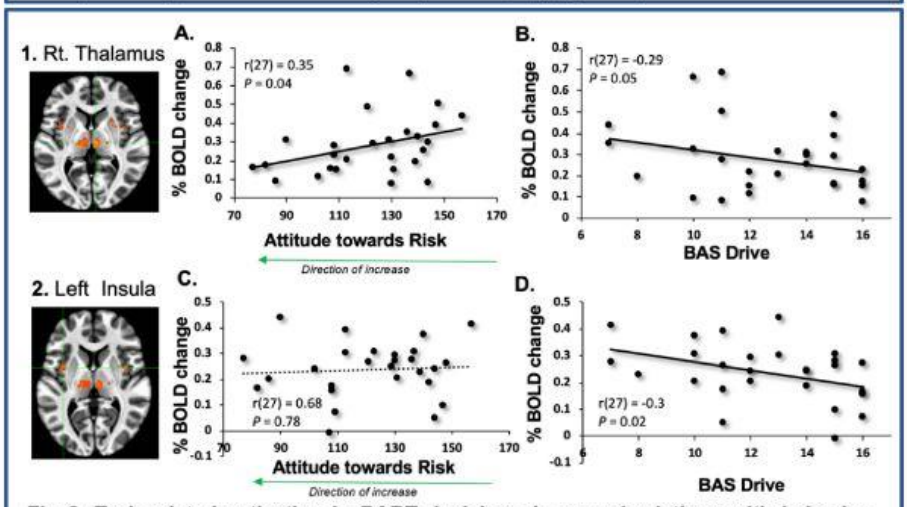

Fig 2. Task related activation in BART decision phase and relations with behavior measures. Decision related activation in right thalamus [1] is correlated with Attitude towards risk [A] and BAS drive [B]. Brain Activation in left insula [2] is correlated with BAS drive [C] but not Attitude towards risk [D].

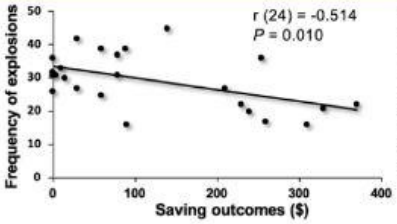

Fig 3. Significant correlation of laboratory performance and real-world behavior. The frequency of explosions (measure or risk) in Balloon Analogue Risk Task significantly correlated with total amount of money saved over the course of 6 months (saving outcomes).

Disclosures: R. Poudel: None. **M.J. Tobia:** None. **M.C. Riedel:** None. **T. Salo:** None. **J.S. Flannery:** None. **L.D. Hill-Bowen:** None. **A.R. Laird:** None. **A.S. Dick:** None. **C.M. Parra:** None. **M.T. Sutherland:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.06/Z8

Topic: H.01. Animal Cognition and Behavior

Support: R01DA036534
R01AG060778
K99 DA041493
McKnight Brain Institute Fellowship

Title: Regulation of risky decision making via activity in dopaminergic neurons in the ventral tegmental area

Authors: *S. L. BLAES[1], C. A. ORSINI[1], H. M. HOLIK[1], S. M. BETZHOLD[1], S. M. SINGHAL[2], C. J. FRAZIER[3], J. L. BIZON[5], B. SETLOW[4];
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Abstract: The ability to decide adaptively between options associated with different rewards and risks is critical for well-being and quality of life, and impairments in this form of decision making are associated with a range of psychiatric disorders. Dopamine signaling plays a critical role in such "risky" decision making, but the contributions of dopaminergic activity to temporally-discrete components of the decision process is not well understood. To address this issue, an optogenetic approach was used to inactivate dopaminergic neuron cell bodies in the ventral tegmental area (VTA) in rats during performance of a risky decision-making task. Male and female tyrosine hydroxylase-cre rats underwent surgery to inject AAV- EF1a-DIO-eNpHR3.0-mcherry (which carries the gene for halorhodopsin) into the VTA. Initial verification experiments indicate robust selectivity of transgene (mCherry) expression for TH+ neurons, and further indicate that light-induced activation of eNpHR3.0 is effective at silencing transduced VTA neurons in a midbrain slice preparation. For behavioral experiments, an optic fiber was implanted during surgery to target the VTA. Rats were then trained in a task in which they made discrete trial choices between a small, "safe" food reward and a large, "risky" food reward accompanied by varying probabilities of footshock punishment as in Orsini et al. (2017). Once stable task performance was achieved, the VTA was optogenetically inactivated during discrete task epochs, including deliberation (the time window between trial initiation and a choice) and during delivery of the various possible choice outcomes. Initial data suggest that inactivating VTA dopaminergic neurons during receipt of the large reward when it was not accompanied by footshock reduces rats' preference for the risky option (i.e., decreased risky choice). These results are consistent with the idea that brief reductions in tonic dopaminergic neuron activity

signal negative reward prediction errors regarding the outcomes of behavior, rendering the actions that led to those outcomes less attractive during subsequent choices. Ongoing experiments are testing effects of VTA inactivation in other task epochs, as well as effects of VTA activation via channelrhodopsin.

Disclosures: S.L. Blaes: None. **C.A. Orsini:** None. **H.M. Holik:** None. **S.M. Betzhold:** None. **S.M. Singhal:** None. **C.J. Frazier:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.07/Z9

Topic: H.01. Animal Cognition and Behavior

Support: R01DA036534
R01AG060778
K99DA041493

Title: Dissecting the role of the nucleus accumbens in risk taking with optogenetics

Authors: *C. A. ORSINI[1], S. M. BETZHOLD[2], A.-R. WHEELER[2], T. W. TEN-EYCK[2], J. SHALLCROSS[2], S. HARDEN[2], S. M. SINGHAL[6], M. SCHWENDT[3], C. J. FRAZIER[4], J. L. BIZON[7], B. SETLOW[5];
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Abstract: Previous work shows that the nucleus accumbens shell (NAcSh) mediates cost/benefit decision making, but its role in decision making involving risk of explicit punishment is unclear. The current experiments addressed this question using both circuit- and cell type-specific optogenetic approaches in rats during a decision-making task involving risk of explicit punishment. In Experiment 1, we tested the hypothesis that input from the basolateral amygdala (BLA) to the NAcSh is necessary to guide choice away from risky options. Rats received intra-BLA infusions of an AAV vector encoding halorhodopsin and optic fiber implants in the NAcSh. Rats were then trained in a risky decision-making task wherein they made discrete trial choices between a small, “safe” reward and a large reward accompanied by varying probabilities of footshock punishment. Using a within-subjects design, BLA projections to the NAc (BLA-NAcSh) were optogenetically inhibited during deliberation (the time between trial initiation and reward choice) and during delivery of the large reward when it was punished (LP). Results show that BLA-NAcSh inhibition during either deliberation or the LP outcome increased choice of the

large, risky reward (increased risk taking), indicating that, during both deliberation and evaluation of the LP outcome, BLA input to the NAcSh is required to bias subsequent choices away from risky options. Experiment 2 used a cell type-specific optogenetic approach to test the hypothesis that neurons expressing dopamine D2 receptors (D2R) in the NAcSh also contribute to choice of safer options. Transgenic rats expressing Cre-recombinase selectively in D2R-containing neurons received intra-NAcSh infusions of an AAV vector encoding floxed halorhodopsin, followed by optic fiber implants in the NAcSh. Optogenetic procedures were identical to those in Experiment 1. Inhibition during deliberation increased risk taking, but inhibition during the LP outcome had no effect on choice behavior. These data provide novel information about the contribution of NAcSh activity to risky decision making. First, the NAcSh receives risk- and reward-related information from the BLA to bias choices toward safer options during deliberation, and to provide negative feedback about choices resulting in punishment. Further, within the NAcSh, activity of D2R-expressing neurons may signal this information during the deliberative process, the integration of which biases choices toward safer options. Future experiments will investigate whether BLA inputs onto D2R-expressing neurons are critical for this latter process.

Disclosures: C.A. Orsini: None. **S.M. Betzhold:** None. **A. Wheeler:** None. **T.W. Ten-Eyck:** None. **J. Shallcross:** None. **S. Harden:** None. **S.M. Singhal:** None. **M. Schwendt:** None. **C.J. Frazier:** None. **J.L. Bizon:** None. **B. Setlow:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.08/Z10

Topic: H.02. Human Cognition and Behavior

Support: MOST Taiwan, 107-2410-H-010 -003 -MY3
MOST Taiwan, 104-2410-H-010 -002 -MY3

Title: High gamma activity in the human prefrontal and insular cortices represent monetary gains and losses during decision making

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Abstract: Many decisions we face involve choosing between options that carry potential gains and losses. Decades of research from psychology show that people are loss averse — the agony incurred by a loss outweighs the pleasure of the same-sized gain. Human fMRI studies showed that many brain regions, including the ventromedial prefrontal cortex (VMPFC), orbitofrontal cortex (OFC) and ventral striatum, represent information about monetary gains and losses during

decision making. It remains controversial, however, whether these regions simultaneously represent gains and losses. In this study, we attempted to address this issue using human intracranial electrophysiology. ***Method.*** In a mixed-gamble task, human subjects (n=13) on each trial faced a 50/50 lottery of a potential monetary gain or loss and had to decide whether to play the lottery. As part of a treatment plan attempting to identify epileptogenic zone, multi-contact depth electrodes were implanted in different brain regions including the OFC, dorsal-to-mid cingulate cortex, amygdala and insula. These four brain regions, with a total of 141 contacts across subjects, were the focus of this study. ***Results.*** We replicated previous findings on loss aversion. Lambda, the ratio of sensitivity to changes in losses to gains inferred from choice behavior was 1.93 (median), close to previous studies (lambda=2). Overall, high-gamma activity in 90% of the contacts in these regions showed gain-only, loss-only, or gain-and-loss representations. However, there were more contacts representing either gain or loss than representing both gain and loss. The proportion of contacts representing only gains was identical to that representing only losses (~ 40%), while a significantly smaller proportion (15%) represented both gains and losses. When examining each region separately, these two statements remain true in amygdala and insula. Dorsal-to-mid cingulate cortex, compared with OFC, amygdala and insula, showed less response to both gains and losses: the ratio of gain-representing contacts in dorsal-to-mid cingulate to all gain-representing contacts was significantly smaller than the ratio of contacts in dorsal-to-mid cingulate to all contacts. The same is true for losses. Together, these results provide more support to the separate encoding hypothesis — that gains and losses are represented by different populations of neurons in these regions than by the same neurons.

Disclosures: **S. Wu:** None. **S. Wu:** None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.09/Z11

Topic: H.02. Human Cognition and Behavior

Support: R56MH113627
K12HD073945

Title: Influence of dopamine on perception of effort

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Abstract: The depletion of dopaminergic neurons in Parkinson's disease has been thought to give rise to motivational deficits that result in a reduced willingness to exert effort to obtain reward. Dopamine signaling is generally considered to mediate these deficits via its influence on reward processing. However, there is little known about the role of dopamine in processing of effort costs and the perceptions of effort. In this study, we investigated the influence of dopamine on the perception of effort by testing persons with Parkinson's, ON and OFF-dopaminergic medication. Participants performed an effort perception task in which they were cued to exert unknown amounts of effort by gripping a hand-held dynamometer, and subsequently rating their perceived exertion on a numerical scale. We found that participants reported exertions to be more effortful in the dopamine depleted condition, as compared to supplemented condition. Moreover, in a trial-wise analysis we found that variability in force production during exertion explained deviations in subsequent effort ratings in the dopamine depleted condition, but not the supplemented condition. A total of 11 participants have been assessed with this paradigm, and subsequent analyses will investigate the role of dopamine in mediating the influence of exertion variability on ratings of perceived exertion.

Disclosures: P. Padmanabhan: None. **R.T. Roemmich:** None. **V.S. Chib:** None.

Poster

512. Economic Decision-Making

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Topic: H.02. Human Cognition and Behavior

Support: NIH GRANT R56MH113627
NIH GRANT K12HD073945

Title: Motor cortical thickness and the subjective valuation of physical effort in humans

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Abstract: The subjective nature of effort critically shapes our decisions to engage in physical activity. For example, if a workout routine feels overly effortful we may decide not to participate, regardless of its potential benefits. One factor that might critically influence subjective perceptions of effort is the inherent anatomy an individual's motor cortex. In this experiment, we investigated the relationship between behavioral preferences for prospective effort and the anatomical properties of motor cortex. We hypothesized that the thickness of a specific region of motor cortex, the hand knob, a region responsible for motor output during

effortful exertions of the hand, would be predictive of an individual's subjective valuations of hand-grip effort. This hypothesis was motived by previous studies that have shown greater cortical thickness is associated with a higher resting motor threshold, suggestive of a diminished capacity to initiate motor action. To study the relationship between motor anatomy and subjective effort preferences, we acquired structural MRI scans of participants brains and had them perform an effort-based decision-making task. To estimate subjective preferences for prospective effort, participants performed a series of risky forced-choices involving two potential options - a low amount of effort, required with certainty, or a risky option that could result in even more effort exertion or none at all (with equal probability). From these choices, we were able to acquire a mathematical parameter which captured individual participants' subjective valuations of prospective effort. Using the structural MRI scans, we traced each participants' hand knob and determined the average cortical thickness of this brain region. We found that the mean thickness of the hand knob was positively correlated with individuals' subjective valuations of effort - those individuals that found effort to be more costly exhibited thicker hand knobs. Critically, subjective effort preferences were not correlated with other dimensions of hand knob anatomy or other brain regions, and hand knob thickness was not related to subjective preferences for reward. These results suggest that the inherent properties of an individual's motor cortical anatomy play a significant role in representations of feelings of effort and decisions to exert.

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Poster

512. Economic Decision-Making

Location: Hall A

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Program #/Poster #: 512.11/Z13

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant 1R01AG058817-01

Title: Brain-behavior correlates of intertemporal choice in healthy aging

Authors: H. ROMERO-KORNBLUM, A. J. BEAGLE, J. KRAMER, *W. CHIONG;
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Abstract: Older adults often face important real-world choices between present and future value. Population-level data indicate that compared with middle-aged adults, older adults use credit disadvantageously; e.g., paying higher interest rates on loans and more frequently incurring fees (Agarwal, Driscoll, Gabaix, & Laibson, 2009). Many previous studies of intertemporal choice in aging have focused on group differences between young and old cohorts (often recruited in

different ways), with conflicting results. In a preregistered study (https://osf.io/hxwvm), we examined cognitive and neural correlates of intertemporal choice within a cohort of 158 healthy adults aged 45-84 (*M*=76). Participants made 92 choices between a smaller immediate and larger delayed reward, in which the absolute magnitude of the delayed reward, delay length, and the relative difference in reward magnitude were orthogonally varied. Subject-level sensitivities to these features, as well as participants' baseline tendency to choose a smaller immediate or larger delayed reward, were estimated using mixed-effects logistic regression (see also de Water et al., 2017). Individual discount rates (k, assuming a hyperbolic function) were also separately estimated via maximum likelihood. In preregistered behavioral analyses, individual discount rates and feature sensitivities were not significantly associated with age or standard measures of executive function. In preregistered VBM (voxel-based morphometry) analyses in 118 subjects with linked T1 MRI images, we found suggestive associations between sensitivity to relative differences in reward magnitude and grey matter volumes in the left (p=0.064, based on cluster extent using a Monte Carlo simulation in 1000 permutations at voxelwise p<0.001) and right (p=0.087) mid-caudate. In an exploratory VBM analysis, individual discount rates (k values) were associated with grey matter volumes in the right frontal operculum (p=0.042; left frontal operculum p=0.130). Our findings suggest that in a rigorously-screened healthy older adult population, age itself and executive function are not associated with disadvantageous intertemporal choice; while atrophy in the caudate and frontal operculum may be associated with such choices.

Disclosures: H. Romero-Kornblum: None. **J. Kramer:** None. **W. Chiong:** None. **A.J. Beagle:** None.

Poster

512. Economic Decision-Making

Location: Hall A

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Program #/Poster #: 512.12/Z14

Topic: H.01. Animal Cognition and Behavior

Support: McKnight Pre-Doctoral Fellowship
Pat Tillman Scholarship
McKnight Brain Research Foundation
R01AG029421
RF1AG60778

Title: Optogenetic inactivation of prefrontal cortex during intertemporal choice reveals unique roles for this structure in young and aged rat decision making

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Abstract: The medial prefrontal cortex (mPFC) is the rodent homologue of human dorsolateral prefrontal cortex and is critical for mediating executive functions such as working memory and cognitive flexibility. These executive functions are important for supporting cost-benefit decision making such as whether to choose an option that yields a small reward delivered immediately versus an option that yields a larger reward that isn't delivered until sometime in the future (intertemporal choice). Previous work from both rats and humans indicates that older subjects reliably prefer large, delayed rewards in comparison to young and these preferences correlate with age-associated impairments in cognitive flexibility. The current study used an optogenetic approach to better define the exact contributions of mPFC to intertemporal choice, and to determine if these contributions change with age. Young adult (6 mo.) and aged (24 mo.) Fischer 344 x Brown Norway F1 hybrid rats were surgically implanted with guide cannulae targeting mPFC, through which pAAV-CaMKIIa-eNpHR3.0-mCherry (halorhodopsin) was delivered and optic fibers were implanted. Rats were subsequently trained on an adjusting-delay intertemporal choice task in which preference for small vs. large rewards was evaluated in the presence of ascending delays to large rewards. Upon reaching stable performance, a within-subjects design was used to inactivate mPFC during discrete phases of choice behavior. In young rats, multiple roles for mPFC in intertemporal choice were identified. mPFC inactivation prior to choices *increased* young rats' preference for the large, delayed reward (made rats less impulsive). In contrast, mPFC inactivation after choices were made (during evaluation of the large, delayed reward) *decreased* rats' preference for the large, delayed reward (made rats more impulsive). In contrast to the effects in young rats, mPFC inactivation during the delay period prior to large reward delivery *increased* aged rats' preference for the large, delayed reward but had no effects during other choice phases. The data suggest that differential engagement of mPFC during intertemporal decision making may help explain robust age differences in intertemporal choice behavior.

Disclosures: C.M. Hernandez: None. **A. Wheeler:** None. **C.C. Labiste:** None. **T.W. Ten Eyck:** None. **B. Setlow:** None. **J.L. Bizon:** None.

Poster

512. Economic Decision-Making

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Program #/Poster #: 512.13/Z15

Topic: H.01. Animal Cognition and Behavior

Support: UF Undergraduate Scholars Program
McKnight Pre-Doctoral Fellowship

Pat Tillman Scholarship
K99/R00 NIDA
McKnight Brain Research Foundation
RF160778
R01AG024671

Title: Contributions of gonadal hormones to intertemporal choice in male rats

Authors: *A.-R. WHEELER[1], C. M. HERNANDEZ[1], C. A. ORSINI[1], T. W. TEN EYCK[1], C. C. LABISTE[1], B. SETLOW[2], J. L. BIZON[3];
[2]Dept. of Psychiatry, [1]Univ. of Florida, Gainesville, FL; [3]Neurosci., Univ. of Florida McKnight Brain Inst., Gainesville, FL

Abstract: Intertemporal choice involves decisions among options that differ in both reward magnitude and delay to reward delivery. All other things being equal, individuals prefer large over small rewards; however, individuals tend to more readily choose small over large rewards the longer they must wait for the large reward (i.e., the value of the large reward is "discounted" by the delay to its delivery). There are marked individual differences in intertemporal choice across the population. Extreme preferences for either small, immediate rewards (greater "impulsive choice") or large, delayed rewards (reduced impulsive choice) are associated with multiple psychiatric disorders. Even outside of pathological contexts, however, variation in intertemporal choice predicts life outcomes such as educational attainment and socioeconomic status.

Gonadal hormones have been proposed to contribute to variation in intertemporal choice both within and between sexes, but there have been relatively few direct tests of this hypothesis. The current study evaluated the contributions of gonadal hormones to intertemporal choice in male rats. Young adult (4 mo.) male Fischer 344 × Brown Norway F1 hybrid (FBN) rats were trained in an intertemporal choice (delay discounting) task in which they made discrete trial choices between levers that yielded a small, immediate reward (1 food pellet) vs. a large reward (3 food pellets) delivered after a delay period. The delays to large reward delivery increased in blocks of trials across each session (0, 10, 20, 40, 60 s delays). Rats were initially trained on the task, then divided into two groups matched for choice behavior that received castration or sham surgery. After recovery, rats were re-tested on the task, and data compared both between groups and before/after surgery. Castration caused an increase in choice of the small, immediate reward (increased impulsive choice) compared to both sham controls and pre-surgical baseline performance. Surprisingly, however, 5 days of subcutaneous injections of a physiological dose of testosterone (125 µg) in castrated rats did not reverse this phenotype, suggesting that the effects of castration on impulsive choice are not mediated solely by reductions in circulating testosterone. Considered together, these data demonstrate a role for testicular hormones in maintaining preference for large, delayed rewards, but that testosterone alone (at least under the conditions tested here) is not sufficient to reproduce this effect.

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Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.14/Z16

Topic: H.02. Human Cognition and Behavior

Title: The neuroeconomics of narratives and asset-price bubbles: Power-law dynamics of asset markets may arise from switching between valuation and control networks

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Abstract: Objective: Narratives (e.g., "housing prices will keep rising", "dot-com stocks are a great investment in a new era", and variations on "this time is different") may drive asset-price bubbles by persuading investors to focus attention on supposedly positive characteristics of assets (Shiller, 2017). Furthermore, narratives may elicit bubble-related herding (Baddeley, 2010; Stiglitz, 2011) by activating an evolutionary predisposition to group behavior seen also in non-human species (Haracz, 2013). Therefore, this review seeks neuroeconomic mechanisms potentially involved in the spread of bubble-related narratives.
Methods: A systematic literature review focused on neuroimaging studies of herding (i.e., social conformity), persuasion, and narrative-influenced attention.
Results: Components of the valuation network (i.e., nucleus accumbens [NA] and ventromedial prefrontal cortex [vmPFC] or nearby orbitofrontal cortex [OFC]) were activated in subjects showing a herding-like change in opinion or behavior (Zaki et al., 2011; Wei et al., 2019). Exposure to persuasive health-related messages was associated with increased connectivity between the NA and vmPFC (Cooper et al., 2017, 2018a; Falk and Scholz, 2018), as well as decreased connectivity in the frontoparietal control network (Cooper et al., 2018b). This connectivity pattern, increased in the valuation network and decreased in the control network, was found relative to healthy controls in individuals with heroin addiction (Xie et al., 2014; Zhai et al., 2015) or internet gaming disorder (Dong et al., 2015), suggesting a tendency for these networks to function alternatively or in opposition. An fMRI study of lab markets indicates that asset-price bubbles and crashes may involve an oppositional relationship between these networks. Lab bubbles were driven by asset buying based on NA activity, whereas crashes were triggered by selling related to anterior insula (AI) activity (Smith et al., 2014). A meta-analysis (Chang et al., 2013) as well as simultaneous fMRI and EEG recordings suggest that the AI may signal the need for deliberation and frontoparietal activity (Hinault et al., 2018). Roles for the NA and AI in mediating asset buying and selling, respectively (Smith et al., 2014), may arise from an involvement of these areas in attention focusing. The NA and AI were activated when subjects were instructed to focus, respectively, on positive or negative aspects of stimuli (Kruschwitz et al., 2018).

Conclusion: Narratives that drive asset buyers and sellers may generate power-law dynamics of bubbles (Preis et al., 2011) by eliciting switches between valuation and control network activity.

Disclosures: J.L. Haracz: None.

Poster

512. Economic Decision-Making

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 512.15/Z17

Topic: H.02. Human Cognition and Behavior

Support: NSFC Grants 31571117 and 31871101

Title: Decoding the time-evolving neural valuation of gain and loss using MEG

Authors: *S. NIE[1], M. WANG[1], H. ZHANG[1,2,3];
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Abstract: In human decision-making under risk, loss is typically valued more than the same amount of gain, a behavioral phenomenon known as loss aversion, which suggests that gain and loss are valuated differently in the brain. Functional MRI studies have identified different brain pathways for the processing of gain and loss but leave the temporal course of valuation unresolved, due to their limited temporal resolution. Here we used magnetoencephalography (MEG) to investigate how the neural valuation of gain and loss in decision-making under risk evolves over time from milliseconds to seconds. On each trial, participants (N = 8) were presented first with a sure amount of monetary payoff and then a sequence of two-outcome gambles (1250 ms per gamble) that might end unexpectedly. Their task was to evaluate each gamble, choosing between the gamble and the sure payoff, but only report their choice for the last gamble in the sequence. Each gamble had a 50-50 chance to yield a gain or a loss, with the values of gain and loss varying independently across gambles. We found loss aversion in participants' behavioral choices: A logistic regression analysis showed that one unit of loss had a larger influence on participants' choices compared to one unit of gain ($t(7) = 2.38$, $p = .049$). For each participant, 306-channel MEG recordings were available for approximately 1250 gambles, from which we extracted 2-16 Hz power spectrum for single time points using time-frequency analysis. We then applied dimension-reduction and regression analysis to the spectrum at each specific delay after gamble onset (in the range of 0 to 1250 ms) to decode the values of gain and loss in the gamble. We found that the cross-validated decoding performance was significantly above chance (two-tailed paired *t*-test $p < .01$, uncorrected) first at 59 ms and 310 ms after gamble onset, respectively for gain and loss. Decoding was on average better for gain before 222

ms and better for loss between 283 and 1156 ms. Our preliminary results suggest that the neural valuation occurs earlier for gain but lasts longer for loss.

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Poster

512. Economic Decision-Making

Location: Hall A

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Topic: H.02. Human Cognition and Behavior

Support: MURI N00014-16-1-2832
NIMH F32 MH116592-01A1

Title: Testing neural representations of value and task space

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Abstract: Adaptive decision-making depends on knowing the value of a choice given current circumstances — i.e. contextual state information. The orbitofrontal cortex (OFC) has long been implicated in the flexible representation of option values. However, recent work has argued that this region may instead represent a 'cognitive map of task space' — that is, information about a latent contextual state that conditionalizes the value of different options. Other work has argued that contextual state information of this kind may be signaled by the hippocampus (HPC), or depends on both of these regions. To test these hypotheses, we crossed hidden contextual state information and expected value in a functional magnetic resonance imaging (fMRI) experiment. Human participants learnt the value of three different image categories (leaves, hands and foods) via feedback in three different context states with distinct category-value associations. Each of these latent contextual states was cued by three different pictures of natural scenes. Participants were then trained on the value of three new image categories (faces, animals and objects) in the presence of one natural scene cue from each state. Finally, in a test phase in the scanner, participants had to transfer information about the value of these new categories to the other two held-out natural scene cues based on their previously established associations with the trained cue, without any new information provided by feedback. Participants' choices showed they were able to leverage abstract information about the latent contextual states to transfer new value associations to these held-out cues. Using representational similarity analysis (RSA), we tested whether OFC and HPC pattern activity carried information about the state-dependent values of options, latent state information needed to infer option values, or both. This experiment contrasts

two major hypotheses regarding the function of the OFC, giving critical insight into the function of this region in guiding flexible behavior.

Disclosures: **A.R. Vaidya:** None. **H. Jones:** None. **D. Badre:** None.

Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: AoE-M09-12, C6004-17G, and C5030-14E
SFARI-510178
31721002, 91632306, and 51627807

Title: Kibra modulates learning and memory via binding to dendrin

Authors: Y. LU[1], *S. MA[2];
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Abstract: Kibra is a synaptic scaffold protein regulating learning and memory. Alterations of Kibra-encoding gene WWC1 cause various neuronal disorders, including Alzheimer's disease and Tourette syndrome. However, the molecular mechanism underlying Kibra's function in neurons is poorly understood. Here we discover that Kibra, via its N-terminal WW12 tandem domains, binds to a postsynaptic density enriched protein, Dendrin, with a nanomolar dissociation constant. On the basis of the structure of Kibra WW12 in complex with Dendrin PY motifs, we developed a potent peptide inhibitor capable of specifically blocking the binding between Kibra and Dendrin in neurons. Systematic administration of the inhibitory peptide attenuated excitatory synaptic transmission, completely blocked long-term potentiation induction, and impaired spatial learning and memory. A Kibra mutation found in Tourette syndrome patients causes defects in binding to Dendrin. Thus, Kibra can modulate spatial learning and memory via binding to Dendrin.

Disclosures: **Y. Lu:** None. **S. Ma:** None.

Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 513.02/Z20

Topic: H.01. Animal Cognition and Behavior

Title: The mechanism study of histone demethylation gene Utx in mouse cognitive function

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Abstract: Epigenetic abnormalities caused by genetic mutation in epigenetic regulators can result in neurodevelopmental disorders, deficiency in neural plasticity and intellectual disability. *Utx* (Ubiquitously transcribed tetratricopeptide repeat, X chromosome, also known as lysine-specific demethylase 6A, KDM6A) is candidate gene for X-chromosome-linked intellectual disability (XLID) which coding histone demethylase.
We focus on the function of *Utx* on the pathogenic mechanism in one specific type XLID-Kabuki syndrome using the *Utx* conditional knockout mice. Previous genetic studies showed that *Utx* is one of the main pathogenic genes in Kabuki syndrome. However, the mechanism about how *Utx* gene causes cognitive dysfunction in Kabuki syndrome remains unclear. We found that *Utx* knockout mice showed the learning and memory deficits in water maze test and contextual fear conditioning. The KO mice also displayed long term potential (LTP) deficits and neuron morphological defects. Mechanistically, we found that the dysfunction of *Utx* caused the downregulation of calmodulin.
Keywords: *Utx*, learning and memory, calmodulin

Disclosures: L. Chen: None. **M. Liu:** None. **X. Yang:** None. **W. Li:** None.

Poster

513. Mechanisms Underlying Memory Formation

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Program #/Poster #: 513.03/Z21

Topic: H.01. Animal Cognition and Behavior

Support: PAPIIT IN215719

Title: Calcineurin modulation of conditioned taste aversion extinction

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Abstract: Nowadays, it is widely accepted that memory extinction involves the formation of a new associative memory that inhibits a previously conditioned association rather than unlearning of acquisition. Nevertheless, the cellular and molecular mechanisms that underlie this process are still unclear. In this regard, it has been suggested that kinases and phosphatases modulate the processes of conditioning and extinction, respectively. A body of evidence suggests that protein phosphatase calcineurin (CaN) is involved in the extinction of some behavioral tasks. Indeed, our previous studies showed that conditioned taste aversion (CTA) extinction increases the CaN expression in the insular cortex (IC). CTA is a well-established learning and memory paradigm in which an animal associates a novel taste with nausea. Meanwhile, the IC is a region of the brain that lies in the temporal neocortex and is known for its role in processing aversively motivated learning tasks, like CTA. The aim of the present study was to evaluate the participation of CaN in the extinction of the conditioned taste aversion. To do so, we infused bilaterally in the IC of adult male Wistar rats, the calcineurin specific inhibitor FK506, 30 minutes before the second extinction session. Our results show that infusion of FK506 elicits an impairment of CTA extinction. That is, CaN inhibition slows down the extinction of CTA, thus revealing that this phosphatase plays an important role on extinction learning, and therefore on the maintenance of CTA.

Disclosures: S.E. Reyes-García: None. **M.L. Escobar:** None.

Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 513.04/Z22

Topic: H.01. Animal Cognition and Behavior

Support: NIMH grant MH078064 to JR

Title: Comparative analyses of cytoskeletal gene expression during sate-dependent memory transition from recent to remote

Authors: *V. JOVASEVIC[1], F. SANANBENESI[3], J. WIKTOROWICZ[4], A. FISCHER[5], J. RADULOVIC[2];
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Neurodegenerative Dis., Göttingen, Germany; [4]Med. Br., The Univ. of Texas, Galveston, TX; [5]Univ. Goettingen/Dzne, Goettingen, Germany

Abstract: Overwhelming stressful experiences can lead to mental illnesses known as dissociative disorders. They are thought to arise when normally integrated functions of consciousness, such as memory, perception, and identity awareness become disrupted. Dissociative symptoms are often debilitating, and persist for a long time after the initial stress has ended. While many dissociative symptoms are intrinsic to human sufferers, and therefore cannot be studied in rodents, this is not the case with dissociative amnesia, which can be modeled in rodents using state-dependent learning. Fear-inducing memories can be state-dependent, meaning that the retrieval of a memory is most efficient when occurring under the same state of consciousness as when the memory was encoded. State-dependent memories are long lasting, and they retain their state-dependence, suggesting that distinct mechanisms initiated at encoding are maintained during consolidation and transition from recent to remote. The cytoskeletal system plays a crucial role in neuronal plasticity, learning and memory, early after encoding. Interestingly, the most over-represented genes differentially expressed under normal and state-dependent conditions at this early stage are those with known function in cytoskeletal architecture. However, changes in the expression of cytoskeletal and cytoskeleton-associated (CCA) genes, and their function during the transition of fear-inducing memories from recent to remote in different states, remains largely unknown. Here we analyzed the global changes in the expression of CCA genes using proteomic and high throughput RNA analyses to identify individual genes which contribute to the transition of fear-inducing memories from recent to remote under normal and state-dependent conditions. Our results show that the consolidation of memories and their transition from recent to remote in different states is accompanied by diverging alterations in the expression of CCA genes belonging to distinct cytoskeleton-mediated cellular processes.

Disclosures: V. Jovasevic: None. **F. Sananbenesi:** None. **J. Wiktorowicz:** None. **A. Fischer:** None. **J. Radulovic:** None.

Poster

513. Mechanisms Underlying Memory Formation

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Topic: H.01. Animal Cognition and Behavior

Support: P50MH100024
Schmidt Science Foundation
Kavli Postdoctoral Fellowship

Title: Imaging endogenous AMPA receptor dynamics underlying fear learning

Authors: *A. R. GRAVES[1], D. J. TWARD[2], M. I. MILLER[2], J. T. VOGELSTEIN[2], R. L. HUGANIR[1];
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Abstract: Synapses are the fundamental unit of the nervous system. They enable rapid communication between neurons and provide a substrate for plasticity that drives adaptive behavior. Synaptic plasticity, the bidirectional control of synapse strength via dynamic regulation of AMPA receptors, is the leading cellular mechanism underlying many cognitive functions, including learning and memory. However, the distribution of memory encoding, storage, and retrieval within vast networks of millions of synapses remains almost completely unknown. Here, we employ in vivo imaging of fluorescently tagged AMPA receptors to directly observe the dynamics of endogenous synaptic networks in retrosplenial cortex during fear learning and recall. These unprecedentedly detailed neural maps reveal that memories are stably stored by complex synaptic networks within retrosplenial cortex.

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Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 513.06/Z24

Topic: H.01. Animal Cognition and Behavior

Title: Tracking metabolic changes associated with retrieval in the hippocampus

Authors: *M. MARUI, K. ADACHI, T. HAYASHI, M. NAGASAWA;
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Abstract: Background: Dementia is one of major diseases in the world today. World Health Organization reported that it is estimated that its subjects exceed 100 million in 2050. Especially, memory impairment, one of the characteristic symptoms of dementia, is an issue and induce the reduction of ‘‘Quality of Life’’. Thus, it needs to be established the therapeutic treatment and prophylaxis of memory impairment. Memory function is consisted of three processes, “encoding’’, “storage’’ and “retrieval’’, and many dementia subjects are impaired their retrieval processes. However, the retrieval mechanism in memory function remains unclear. The present study aimed to elucidate the mechanism for retrieval process using a retrieval-induced model , especially it was focused on the transition of metabolites levels in the brain depending on the time course from the onset of retrieval. Material and Method: Object recognition test (ORT) with some modifications was performed for a retrieval-induced model. Male 8-week-old ICR mice

were allowed to explore in the black square arena with two identical objects for 5 min. This trial was performed once a day for 3 days. On 4th day, control (CON) mice explored the familiar objects, while ‘‘memory retrieval’’ (MR) mice explored an identical object and a novel object. The duration for exploration in these trials were 1 min, 3min or 5min. Mice have an interest in a novel object. Accordingly, a ratio of duration for exploring a novel object on 4th day, an index of retrieval-based behavior of MR mice was calculated form the following formula; 100 × duration for exploring a novel object /duration for exploring both objects. In CON mice, the expediential index was estimated by a similar method. After these trials, mice were sacrificed under anesthesia and their hippocampi were immediately dissected from their whole brain. Metabolites in the hippocampus were determined by GC-MS, and those levels were compared with each time point for exploration. Result: A ratio of duration to explore a novel object of MR mice was significantly higher than those of CON mice in all time points, approximately MR mice showed 70% and CON mice showed 50%. This result indicates that MR mice recalled a familiar object at any time point. In metabolome analysis, glutamate showed different levels in each time point. Additionally, it suggested that glycine production was accelerated. Glutamate and glycine regulate the function of N-methyl-D-aspartate (NMDA) receptor which related to memory function. Present study demonstrated that the metabolites which regulate NMDA receptor function altered depending on the duration for retrieval and partial mechanism of retrieval was revealed.

Disclosures: **M. Marui:** None. **K. Adachi:** None. **T. Hayashi:** None. **M. Nagasawa:** None.

Poster

513. Mechanisms Underlying Memory Formation

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Topic: H.01. Animal Cognition and Behavior

Support: NIH T32 ES007051

Title: Developmental deltamethrin exposure to Sprague-Dawley rats alters dopaminergic and glutamatergic systems and long-term potentiation when tested as adults

Authors: *E. M. PITZER[1], C. SUGIMOTO[2], G. A. GUDELSKY[3], M. T. WILLIAMS[1], C. V. VORHEES[1];
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Abstract: Pyrethroids are a prevalent class of synthetic insecticides that act through voltage gated sodium channels to prolong channel opening leading to depolarization. Pyrethroids are

used in many settings where children are present, such as schools and parks, as well as for treating head lice. Epidemiological studies find that developmental exposure to pyrethroids is associated with neurological and behavioral abnormalities. The effects of Type II pyrethroids, such as deltamethrin (DLM), on development have received relatively little attention. We showed that Sprague-Dawley rats exposed to DLM from postnatal day (P)3-20 had deficits in egocentric and allocentric learning and memory as adults. We also observed increased hippocampal long term-potentiation (LTP) at P28-35 in DLM-treated rats. Here we exposed Sprague-Dawley rats to 0 or 1.0 mg/kg/day DLM by gavage from P3-20. LTP was assessed at P60-90 in brain slices in CA1. Males treated with DLM had increased LTP in the CA1 region compared with controls ($p < 0.0001$). Females treated with DLM had slightly decreased LTP compared with controls ($p < 0.05$). Amphetamine-stimulated dopamine release was assessed via microdialysis. DLM-treated rats exhibited decreased dopamine release in the nucleus accumbens ($p < 0.05$). Currently potassium stimulated glutamate release is being tested in the hippocampus. Western blots revealed that DLM-treated rats did not differ in dopamine receptor D1 (DRD1) protein in the n. accumbens or hippocampus, but was increased in the neostriatum of male but not female rats ($p < 0.05$). No differences were observed for DRD2 levels or for NMDA-NR1. However, NMDA-NR2B protein was decreased in the neostriatum of male DLM-treated rats ($p < 0.05$). A trend was observed for increased NMDA-NR2A protein in the hippocampus of male DLM-treated rats ($p < 0.10$) compared with controls. No dopamine or NMDA receptor related changes were observed in female DLM-treated rats. The results indicate that rats developmentally exposed to DLM have altered CA1 LTP, decreased extracellular n. accumbens dopamine release, increased DRD1 and decreased NR2B protein in neostriatum. These DLM effects are consistently male-specific. Experiments testing the effects of developmental DLM exposure on dopamine and glutamate release in other regions and expression of apoptotic markers are in progress.

Disclosures: E.M. Pitzer: None. **C. Sugimoto:** None. **G.A. Gudelsky:** None. **M.T. Williams:** None. **C.V. Vorhees:** None.

Poster

513. Mechanisms Underlying Memory Formation

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Neurogenomics 2CI Fellowship to D.W.Y.

Title: Characterization of behavioral deficits in activity-regulated cytoskeleton-associated protein knock-in (ArcKR) mice

Authors: *D. W. YAKOUT[1], Z. D. ALLEN[1], A. J. GEORGE[1], F. P. TALLARD[1], J. SEXTON[1], S. S. MOY[2], A. M. MABB[1];
[1]Neurosci. Inst., Georgia State Univ., Atlanta, GA; [2]Dept. of Psychiatry and the Carolina Inst. for Developmental Disorders, Univ. of North Carolina, Chapel Hill, NC

Abstract: The induction of activity-regulated cytoskeleton-associated protein (Arc) is correlated with neural activity, which is critical for learning and memory consolidation. Upon induction, Arc is rapidly degraded by the ubiquitin-proteasome pathway. However, the significance of Arc degradation on memory processes has been poorly characterized. The endosomal-associated E3 ubiquitin ligase, TRIAD3/RNF216 ubiquitinates Arc at Lysines 268 and 269, which is necessary for its proteasome-dependent degradation. To test the role of TRIAD3/RNF216-dependent effects on Arc degradation, we previously generated a transgenic mouse-line (ArcKR). In ArcKR mice, TRIAD3/RNF216-dependent Arc ubiquitination sites are mutated to Arginine, thus interfering with Arc degradation. Although memory acquisition was intact, ArcKR mice have specific deficits during reversal learning in a Barnes Maze spatial memory task. Here, we continue to characterize behavioral deficits in ArcKR mice, elucidating the role of TRIAD3/RNF216-dependent Arc removal in sensorimotor integration, associative learning, social memory, attention, and depression-like behaviors. Additionally, we examine Arc patterning in ArcKR mice in brain regions associated with the tested behaviors such as the hippocampus, orbitofrontal cortex and medial prefrontal cortex.

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Poster

513. Mechanisms Underlying Memory Formation

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Title: Overexpression of purinergic P2X4 receptors in hippocampus rescues memory impairment of rats with type 2 diabetes

Authors: P.-A. ZHANG[1], Q. SUN[1], R.-X. WENG[1], H.-H. ZHANG[1], S. YU[2], ***G.-Y. XU**[1];
[1]Soochow Univ., Suzhou, China; [2]Anesthesiol., Emory Univ. Sch. of Med., Atlanta, GA

Abstract: Aims: More and more cognitive dysfunction has seriously affected the life quality of patients with diabetic mellitus (DM). The pathogenesis of the diabetic cognition impairment remains largely unknown. Purinergic receptors have been reported to be involved in brain high function and related disorders. The present study aims to explore roles of purinergic receptors and mechanisms underlying the diabetic memory impairment in rats with type 2 diabetes mellitus (T2DM). **Methods:** T2DM model was induced in rats fed with high fat diet for 2 weeks followed by intraperitoneal injection of streptozotocin and confirmed by fasting blood glucose and insensitivity to insulin treatment. T-maze and Morris water maze (MWM) tests were used to detect learning and memory. Immunofluorescence and Western blot were used to determine the location and expression purinergic receptors. DNA damage was detected by Long Amplicon Polymerase Chain Reaction (LA-PCR). **Results:** T2DM rats exhibited a significantly lower correct choice rate, higher win-shift failure and Lose-shift failure in the T-maze test, and the less passing times, less time in the quadrant, more mean distance in MWM test than in the age-matched control rats. P2X4Rs were dramatically reduced in the hippocampus of T2DM rats. LA-PCR showed that DNA amplification of *p2x4r* gene in the hippocampus was significantly less in T2DM rats than in control rats. P2X4Rs positive microglia in hippocampus was reduced and the number of activated microglia was significantly increased in T2DM rats compared to controls. Intraperitoneal injection of minocycline significantly reduced the number of activated microglia in the hippocampus and the mean distance in MWM test. Most importantly, overexpression of P2X4Rs markedly suppressed the activated microglia, reduced the expression of TNF-α and IL-1β and reinstated the memory impairment of T2DM rats. **Conclusions:** T2DM leads to excessive activation of microglial cells in the hippocampus, which is most likely mediated by the downregulation of P2X4Rs due to the DNA damage, thus contributing to memory impairment. Overexpression of P2X4Rs might be a potential strategy to rescue memory impairment.

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Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

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Program #/Poster #: 513.10/Z28

Topic: H.01. Animal Cognition and Behavior

Support: NHMRC APP1070081

Title: The role of vitamin D in the adult brain

Authors: M. M. AL-AMIN, R. K. P. SULLIVAN, Y. YU, J. LUI, X. CUI, ***T. H. BURNE**; Queensland Brain Inst., Brisbane, Australia

Abstract: Vitamin D deficiency is a global public health burden, affecting millions of people worldwide. Low serum vitamin D levels are associated with many neuropsychiatric diseases, such as schizophrenia, autism and depression. In these diseases, impaired hippocampal function has been reported as a central issue. The hippocampus is an important brain region contributing to spatial learning and memory, partly by consolidating short to long term memory. Vitamin D may have a specific role in the hippocampus, since neurons in the hippocampus and its various subfields express the vitamin D receptor (VDR). In this study we examined spatial memory impairment in adult vitamin D-deficient BALB/c mice and its underlying mechanism by measuring spine density, perineuronal nets and GABAergic interneuron density in the hippocampus. We also examined the molecular changes in gene expression. Adult male BALB/c mice were fed a control or vitamin D deficient diet for 20 weeks. We showed that AVD-deficient BALB/c mice took significantly longer to learn to avoid the shock zone than control mice over 5 days. All mice performed similarly on the last day of training, demonstrating that AVD deficiency produced a delay in learning. We found a reduction in the spine density in the CA1 region of the hippocampus of AVD-deficient mice. However, there was a significant reduction in the number of cells that immunostained positive for perineuronal nets and neural nitric oxide synthase in all subfields of the hippocampus. The molecular changes were restricted to reductions in the expression of VDR and tyrosine hydroxylase mRNA. Therefore, we can show that adult vitamin D deficiency is associated with impaired spatial learning and altered hippocampal function in mice. We were able to show that chronic vitamin D supplementation prevented the decline in spatial learning, showing that vitamin D supplementation for a prolonged duration may be required to restore hippocampal-dependent function. This research has important public health implications because vitamin D deficiency can be treated.

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Poster

513. Mechanisms Underlying Memory Formation

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Program #/Poster #: 513.11/Z29

Topic: H.01. Animal Cognition and Behavior

Support: Program of the Russian Academy of Sciences

Title: The role of epigenetics in regulation of promoter competition of Prkcz gene

Authors: *A. BORODINOVA[1], P. M. BALABAN[2];
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Abstract: Memory mechanisms require synergic functioning of many intracellular molecular systems, but until recently neither of them was shown to be selectively involved in the learning process. However, in the last decades the neuron-specific product of *Prkcz* gene (protein kinase Mz) was characterized as the necessary and sufficient molecule for memory formation and maintenance. Multi-promoter organization of the *Prkcz* gene enables to selectively transcribe either a short (PKMz) or a long (PKCz) isoform in a tissue-specific manner. However, the molecular mechanism of the region-specific *Prkcz* expression is still uncharacterized. The main idea of this study was to uncover and extend the principles and mechanisms of tissue-specific expression of *Prkcz* transcripts. In the recent article (Borodinova et. al., 2019) we have demonstrated that chromatin rearrangements, induced by histone deacetylase inhibitors (trichostatin A, TSA; sodium butyrate), can influence transcription of the Prkcz gene and shift the natural balance of expression of different Prkcz isoforms in neurons. Analysis of the promoter regions of Prkcz gene demonstrated significant increase in histone acetylation levels in both upstream and downstream promoters that was detected 4 h after the application of TSA, and persisted up to 19 h. Remarkably, we revealed a significant enrichment of H3K4me3 mark of the transcriptionally active regions specifically in the upstream Prkcz promoter that is responsible for synthesis of the PKCz. We showed previously that TSA-induced changes in expression of PKMz and PKCz, were abolished in the presence of protein synthesis inhibitor anisomycin, applied 1 hour before TSA administration, which means that the epigenetically regulated patterns of expression of PKMz and PKCz, reflecting activity of alternative promoters of the Prkcz gene, were controlled by protein synthesis-dependent mechanisms. To find the critical time window during which the specific proteins are necessary for regulation of the PKMz/PKCz transcription, we performed the series of experiments, where anisomycin was applied at different time points after the TSA administration (30 min, 4 h, 6 h). We found that the epigenetic regulation of PKMz/PKCz expression was abolished in the presence of anisomycin applied at all indicated time points, suggesting that synthesis of the specific proteins can be a necessary and limiting step in the epigenetically-triggered competition of Prkcz promoters. Therefore, the identification of genes encoding the described protein regulators that participate in the Prkcz promoter competition requires additional experiments.

Disclosures: A. Borodinova: None. **P.M. Balaban:** None.

Poster

513. Mechanisms Underlying Memory Formation

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Title: TET1 is expressed as two distinct isoforms in the mouse brain with differing effects on physiology and cognitive function

Authors: C. B. GREER[1], S. P. MORAN[1], J. WRIGHT[1], J. D. WEISS[1], P. J. KINGSLEY[2], K. S. CHRONISTER[1], J. ZHU[1], A. Y. JIN[1], L. J. MARNETT[3], A. J. KENNEDY[4], ***G. A. KAAS**[1]; [1]Pharmacol., [2]Biochem., [3]Biochemistry, Chemistry, Pharmacol., Vanderbilt Univ., Nashville, TN; [4]Chem., Bates Col., Lewiston, ME

Abstract: Recently, using a number of different experimental techniques, we have discovered that the *Tet1* gene locus is actually expressed as two distinct mRNA transcripts within the mouse brain. The first, *Tet1 Long* (*Tet1L*), encodes for the previously-annotated canonical *Tet1* enzyme which contains a CXXC, Cysteine-rich and DSBH domain, while the second, *Tet1 Short (Tet1S)* is expressed from an intronic region located ~0.5 kb upstream of *Tet1L* exon 3 and encodes for a truncated enzyme lacking the N-terminal coding region. Using both *in situ* hybridization and qRT-PCR, we detected each transcript throughout the mouse brain and found *Tet1S* mRNA levels to be ~10-20 times greater than *Tet1L.* In addition, the two isoforms both show substantial differences in regards to their transcriptional responses to neuronal activity, sub-cellular protein localization and enzymatic activities. Similarly, RNA and Genome Wide Bisulfite seq (GWBS) data generated from primary hippocampal cultures either overexpressing or repressing these *Tet1* isoforms further support the notion that the function of these enzymes is not redundant. In fact, a large portion of the differentially expressed genes and differentially methylated regions were unique to each *Tet1* isoform. Behaviorally, we found that viral-mediated manipulations of the long isoform led to memory impairment, whereas loss of *Tet1S* did the opposite. Electrophysiological recordings from *Tet1* isoform-altered hippocampal slices revealed significant changes in Long-term potentiation (LTP), which correlated strongly with experimental groups that also exhibited cognitive changes. Overall, our data strongly indicate that these two TET1 enzymes provide important functions in the adult brain, through their unique attributes, gene targets and effects on physiology and cognition. Given that many of the early TET1 studies were done using tools that disrupted both isoforms, it will be important going forward to untangle which of the previous observations result from *Tet1L*, *Tet1S* or both.

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Poster

513. Mechanisms Underlying Memory Formation

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Support: NIH NIMH R01MH106623

Title: Convergent roles of beta-catenin and APC in regulating mRNA translation, plasticity and learning

Authors: *J. M. ALEXANDER, S.-X. JIN, L. A. FEIG, M. H. JACOB;
Neurosci., Tufts Univ. Sch. Med., Boston, MA

Abstract: Intellectual disabilities (ID, IQ<70) are a prevalent brain disorder, affecting 2-3% of the population. Although there are numerous human ID risk genes, the malfunction of convergent processes essential to synaptic plasticity and function, such as local protein synthesis, are thought to underlie the disorder. Our findings identify a new mechanism regulating neuronal mRNA translation, centered on β-cat (β-catenin) and its primary negative regulator in the canonical Wnt signaling pathway, APC (adenomatous polyposis coli protein). APC is also an RNA-binding protein (RNP) (several of its targets are ID-linked genes), and it localizes to RNA-granules with other RNPs such as Fragile-X Mental Retardation Protein (FMRP). We propose novel convergent roles for β-cat and APC in regulating translation with major impact on cognitive function. To test this hypothesis, we generated a mouse that conditionally (CamKIIα-Cre) expresses an N-terminally truncated β-cat in forebrain neurons; this construct closely resembles that produced endogenously by NMDA-mediated Ca^{++} influx stimulating calpain cleavage of β-cat. We used multi-disciplinary approaches (biochemical,n=3-6 per genotype [p.g.], behavioral, n=10-14 p.g. and electrophysiological, n=6-8 p.g. techniques, adult mice [2-4 months old] of both sexes in equal amounts, with Cre-negative littermates as controls). We show that truncated β-cat strongly associates with APC (by co-immunoprecipitation), causes APC hyperphosphorylation, and alters APC binding to and translation of its target mRNAs (altered levels of new protein synthesis). Compared with control littermates, these mice exhibit severe intellectual disabilities and reduced synaptic plasticity consistent with their decreased surface membrane levels of several glutamate receptor subunit subtypes. Intriguingly, we show that truncated β-cat also associates with FMRP (an RNA-binding protein critical for cognition) and this interaction is dependent on the presence of APC.
We propose a new mechanism whereby modification of the Wnt/APC destruction complex and calpain cleavage of endogenous β-cat regulate the mRNA binding and translational functions of APC and potentially other associated RNPs such as FMRP. Our findings identify novel convergent roles of β-cat and APC in regulating translation of synapse associated proteins, and suggest that dynamic, tight regulation of truncated β-cat levels is essential for normal plasticity and learning.

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Poster

513. Mechanisms Underlying Memory Formation

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Title: Targeting Tet2 enhances spatial memory

Authors: *A. REDA[1], A. E. PRATT[1], S. RAUF[1], K. E. ZENGELER[1], H. C. SMITH[1], C. P. GETTENS[2], B. G. MALACHOWSKY[2], A. J. KENNEDY[1];
[1]Neurosci., [2]Chem. and Biochem., Bates Col., Lewiston, ME

Abstract: Active and dynamic DNA methylation in the hippocampus is required for the formation, maintenance, and recall of memories. Here, we demonstrate that enhancing the fidelity of DNA methylation in the CA1 of the hippocampus enhances the strength and lifetime of object location memory in mice. Specifically, DNA demethylation in the CA1 of the hippocampus is mediated by ten-eleven translocation 2 (*Tet2*), which appears to negatively regulate spatial memory function. Conversely, a *Tet2* knockdown or knockout enhances long-term and remote object location memory, and results in the hypermethylation of learning-associated genes. Taken together, these data suggest that *Tet2* negatively regulates hippocampal long-term memory by active demethylation of the genome.

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Poster

513. Mechanisms Underlying Memory Formation

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NIA AG057947

Title: Enhanced response learning with intrastriatal infusions of a BDNF mimic, 7,8-dihydroxyflavone

Authors: M. T. AMBALAVANAR, ***R. S. GARDNER**, P. E. GOLD, D. L. KOROL;
Biol., Syracuse Univ., Syracuse, NY

Abstract: Mature brain-derived neurotrophic factor (BDNF) is a secretory neurotrophin known to activate signaling cascades through phosphorylation of the tropomyosin receptor kinase B (TrkB). Activation of TrkB by BDNF is implicated in synaptic plasticity and hippocampus-sensitive learning and memory. However, the role of BDNF and its downstream signaling in modulating other forms of learning and memory has received less attention. We previously found that exercise, either cognitive or physical, enhanced not only hippocampus-sensitive learning but also striatum-sensitive learning. Enhancement of both types of learning relied on BDNF signaling. Here, we tested the effects of pre-training striatal infusions of the TrkB agonist, 7,8-dihydroxyflavone (7,8-DHF) on striatum-sensitive learning in 3-mo-old male rats. Specifically, we infused several doses of 7,8-DHF (1, 5, or 10 µg / hemisphere) or dimethyl sulfoxide (vehicle) into the dorsolateral striatum 20 min prior to 75 training trials on a response maze that is sensitive to striatal manipulations. During response training, rats learn to use a body turn (right or left) to reach a food reward. The results showed that 7,8-DHF at all doses significantly reduced the number of trials to reach a learning criterion of 9/10 correct consecutive trials from 50±4 (mean±sem) trials in controls to 23-30±~3 trials in 7,8-DHF-treated rats. 7,8-DHF at all doses also significantly increased choice accuracy across the 75 trials of training. These findings add the striatum to those memory systems for which activation of TrkB receptors enhances learning and memory and support the hypothesis that TrkB activation at the time of a learning experience contributes to cognitive performance. The results also reveal a rapid effect on learning of activation of the TrkB receptor, suggesting that neurogenesis associated with BDNF may not be necessary for cognitive enhancements.

Disclosures: R.S. Gardner: None. **M.T. Ambalavanar:** None. **P.E. Gold:** None. **D.L. Korol:** None.

Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 513.16/Z34

Topic: H.01. Animal Cognition and Behavior

Support: CNPQ/Universal 2018

Title: Myosin IIB as a key player in memory maintenance

Authors: *L. DE OLIVEIRA ALVARES[1], M. SILVA[2];
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Abstract: Synaptic plasticity events are intrinsically linked to dendritic spines and both are substrates for the formation, storage and expression. Myosin IIB is a main component for the morphophysiology of the dendritic spines and synaptic regulation. Here, we used blebbistatin (Blebb) to pharmacologically block myosin IIB activity to assess the effects of its inhibition on distinct memory processes. We first found that immediate post-training infusion of blebb in the hippocampus impaired long-term fear memory consolidation, but not short-term memory. Next, we showed that pre-test infusion of the drug hindered memory retrieval. Surprisingly, we also found that blebb was able to suppress memory retention when applied after the consolidation window, even without reactivation. We then replicated those results in a number of other behavioral protocols involving different brain structures and memory tasks. Thus, our results show that Myosin IIB plays an essential role not only in memory formation and expression, but also memory maintenance through its crucial dynamics with actin filaments in the dendritic spines.

Disclosures: L. De Oliveira Alvares: None. **M. Silva:** None.

Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant MH102703

Title: Phosphorylation of 4EBP2 affects hippocampus-dependent memory

Authors: *I. K. SUCCI, N. A. BURKERT, T. JENKINS, J. C. TUDOR;
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Abstract: The hippocampus is a region of the brain critical for memory and cognition. Hippocampal neurons require protein synthesis for memory formation. Lack of sufficient protein synthesis impairs hippocampal-dependent memory consolidation. The mammalian target of rapamycin (mTOR) signaling pathway is a key pathway in protein synthesis. We developed a mutant phosphodefective 4EBP2 adeno-associated virus (AAV) with a CamKII alpha promoter

fragment to selectively express it in excitatory neurons in the hippocampus. Point mutations to alanine residues at the phosphorylation sites of 4EBP2 were to prevent phosphorylation. Mice exposed to the phosphodefective AAV experienced memory deficits compared to control mice. This indicates that phosphorylation of 4EBP2 is necessary in hippocampal-dependent memory consolidation. To further this investigation, we developed a mutant phosphomimetic 4EBP2 adeno-associated virus (AAV) with mutations to the aspartate residues at the phosphorylation site to mimic phosphorylation. Expression of the phosphomimetic AAV did not enhance memory in comparison to control animals. Our findings further support the importance of protein synthesis and mTOR signaling in memory consolidation.

Disclosures: **I.K. Succi:** None. **N.A. Burkert:** None. **T. Jenkins:** None. **J.C. Tudor:** None.

Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

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Program #/Poster #: 513.18/Z36

Topic: H.01. Animal Cognition and Behavior

Support: University of Michigan Office of Research Pilot Faculty Grant

Title: Poly I:C has sex-specific effects on learning and memory systems

Authors: *C. K. POSILLICO, R. E. GARCIA-HERNANDEZ, J. AHMED, S. JACOB, N. C. TRONSON;
Univ. of Michigan, Ann Arbor, MI

Abstract: The neuroimmune system is critical for normal neural processes, including synaptic plasticity and memory formation, and in the regulation of these processes during illness. For example, neuroimmune activation and cytokine signaling impair hippocampal-dependent memory. Here, we used intracerebroventricular (ICV) administration of polyinosinic:polycytidylic acid (poly I:C) to determine the modulation of circuit and molecular mechanisms of memory across multiple memory systems in both males and females. We first examined the activation of the hippocampus during context fear conditioning memory consolidation. Counter to expectations that poly I:C administration would result in decreased activation of context-fear related brain regions, correlating with diminished fear memory, females treated with poly I:C showed exaggerated cFos levels in dorsal hippocampus after context fear conditioning. This suggests that memory deficits as a consequence of neuroimmune activation is not due to suppression of neuronal activity, but rather a shift in the molecular mechanisms, learning strategies, or memory systems engaged. To identify specific effects of neuroimmune activation across multiple memory systems, we used a place-vs-response T-maze task, with a dark escape box as the goal to eliminate confounding effects of immune and

hormonal signaling on food-motivated behavior. Thus, this escape-motivated task is an effective tool for studying simultaneous modulation of hippocampal and striatal learning and memory processes after neuroimmune challenge. Sex differences in poly I:C-modulation of memory may be due to sex-specific neuroimmune response to this immune stimulant. We found that, as expected, ICV poly I:C increased levels of hippocampal cytokines in both sexes, but with stronger activation of CXCL10 in females and CCL2 in males. Neuroimmune function is strongly implicated in disorders of memory such as post-traumatic stress disorder and Alzheimer's disease, and women are twice as likely to develop these disorders compared to men. Uncovering the underlying mechanisms of immune modulation of memory processes in both sexes is thus essential for the development of novel prevention and treatment strategies for memory disorders in both sexes.

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Poster

513. Mechanisms Underlying Memory Formation

Location: Hall A

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Program #/Poster #: 513.19/Z37

Topic: H.01. Animal Cognition and Behavior

Title: Duration of aromatase inhibition differentially affects levels of a postsynaptic scaffolding protein in highly estrogenic female and male hippocampal tissue

Authors: T. COURT[1], C. GUSHO[1], ***D. BAILEY**[2,1];
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Abstract: The estrogen (estradiol, E2)-synthesizing enzyme aromatase is abundant in the hippocampus (HP) of vertebrates, including humans. Brain-derived E2 is important to memory function, and given pronounced sex differences in aromatase expression, this is especially of interest in regard to memory decline following drug treatment in clinical settings. For example, aromatase inhibitors, used to treat estrogen receptor-positive breast cancer, may produce cognitive impairment like forgetfulness. A unique model to examine the direct effects of aromatase inhibition on sexually dimorphic cognitive function and synaptic structure is avian HP tissue. The HP in birds is located on the dorsal surface, so manipulation of neuronal aromatase can be done *in vivo* without the confound of upregulation of the enzyme in glia. Aromatase is localized primarily in axon terminals in the HP, in higher concentration in males than females, and inhibition in males impairs spatial memory acquisition and performance consistent with lesions of the structure. The local E2 synthesized presynaptically can act postsynaptically via G protein-coupled estrogen receptors (GPER). Antagonism results in failure of spatial memory acquisition, and together aromatase inhibition with GPER agonism result in behaviors similar to

controls. Moreover, levels of a postsynaptic scaffolding protein, PSD95, are low in HP tissue treated with an aromatase inhibitor, suggesting a means whereby locally-synthesized E2 and GPERs modify receptor activity or transduction pathways to increase synaptic strength. The current study examined varying durations of aromatase inhibition in adult male and female zebra finch HP tissue. Bilateral craniotomies were made over the HP, and pellets containing the lipophilic aromatase inhibitor 1,4,6-androstatriene-3,17-dione (ATD) were placed and affixed to rest on the brain's surface. Animals were euthanized at 3, 7, and 14 days (d) post-implant, the HP was microdissected, and PSD95 levels were analyzed by Western blot. Levels of PSD95 were significantly ($p < 0.05$) lower in females than in males at 3 d and 14 d but not 7 d. Protein levels were low at 3 d in females but increased at 7 d and were maintained. In males, expression at 3 d did not differ from the 7 d treatment, but there was a significantly higher concentration at 14 d than 7 d. Thus, aromatase inhibition affects PSD95 levels to a greater extent in the female HP initially, perhaps due to a greater aromatase availability in male tissue. Additional work is examining other postsynaptic proteins as well as those promoted by the genomic actions of E2.

Disclosures: T. Court: None. **C. Gusho:** None. **D. Bailey:** None.

Poster

513. Mechanisms Underlying Memory Formation

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Title: Targeting DNA methylation to improve long-term memory in a model for intellectual disability

Authors: L. GALE, J. SERRANO, A. REDA, K. ZENGELER, H. C. SMITH, *A. J. KENNEDY;
Bates Col., Lewiston, ME

Abstract: Active DNA methylation is necessary for some forms of long-term memory function, including spatial and episodic memory. Here we demonstrate that inhibiting the de-methylation of DNA prolongs long-term memory maintenance and is a potential therapeutic target to treat memory deficits associated with intellectual disability. We knocked out Tet genes (Tet1 or Tet2), that encode for cytosine demethylases, from the neural tissue of both neurotypical mice and a mouse model for Pitt-Hopkins Syndrome, an ultra-rare intellectual disability on the autism

spectrum. Tet knockout enhanced long-term memory function, extended memory recall capacity, and rescued memory deficits in Pitt-Hopkins mice at long-term time points. These data suggest Tet enzyme inhibitors might be therapeutically useful in the treatment of Pitt-Hopkins Syndrome and other like intellectual disabilities.

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Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.01/Z39

Topic: H.01. Animal Cognition and Behavior

Support: NIMH Intramural Research Program

Title: Monkeys with orbitofrontal cortex lesions show normal pupil responses and eye movement patterns when viewing valuable images

Authors: *J. HWANG, P. L. NOBLE, E. GONZALEZ-ARAYA, E. A. MURRAY;
Section on Neurobio. of Learning and Memory, Lab. of Neuropsychology, NIMH/NIH, Bethesda, MD

Abstract: Evidence from neurophysiological studies in macaques indicates that neurons in the orbitofrontal cortex (OFC) encode the values of anticipated foods and fluids associated with visual stimuli, and these value signals are modulated by gaze and attention. It is not well understood yet how gaze and/or attentional modulation of neuronal activity in OFC guides behavior, and in what circumstances OFC neuronal activity is necessary. To investigate the causal contribution of OFC to visual exploration of valuable objects, we trained rhesus monkeys with bilateral excitotoxic OFC lesions (N = 3) and unoperated controls (N = 4) on a preferential viewing task. The lesions were intended to include OFC areas 11, 13 and 14, and placement of injections of ibotenic acid was verified using T2-weighted MR scans. The experiment occurred in two stages: stimulus-reward association training and preferential viewing test. We first showed the monkeys 60 images, one at a time. The monkey's job was to look at each image for 2 s, at which time a fluid reward was delivered. Thirty images were followed by a large reward (high-value images) and the other thirty, by a small reward (low-value images). This stimulus-reward association training was given at the rate of 480 trials per day for 5 days. When the training stage was completed, we administered a preferential viewing test. On each trial, two images—one high-value image and one low-value image—were presented simultaneously and the monkeys were allowed to freely view them for 4 s. The only requirement was that the monkey's gaze stay within the boundaries of the two images for the full 4 s. In this stage, an

intermediate amount of fluid was delivered at the end of every trial. All possible pairings of high- vs. low-value images were presented. We collected several behavioral measures, including pupil response, the category of image that captured the 'first look', proportion of viewing time, and the total number of fixations. Both groups showed a consistent preference for the high-value images. During the training stage, the monkeys aborted fewer trials and exhibited greater pupil dilation for high-value relative to low-value images. During the preferential viewing test, when both a high- and a low-value image were available, monkeys looked at the high-value image first on 80% of trials. In addition, monkeys viewed the high-value images 3.7 times longer and made 3.5 times more fixations relative to the low-value images. There was no group difference on any of these measures. Our findings indicate that, at least when stimulus-value associations are acquired postoperatively, OFC is not necessary for guiding the eyes to valuable images.

Disclosures: J. Hwang: None. **P.L. Noble:** None. **E. Gonzalez-Araya:** None. **E.A. Murray:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Title: Contribution of the orbitofrontal cortex to inference based on specific stimulus-reward relationships

Authors: *M. OGAWA[1], S. ISHINO[1], K. TOKUOKA[2], T. ISA[2], B. D. ALLEN[3], A. S. CHUONG[3], E. S. BOYDEN[3], N. OISHI[1], I. SANGHUN[4], T. YAMADA[1];
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Abstract: In classical appetitive conditioning, a neutral stimulus that initially has no effect on a subject is repeatedly followed by reward (or no reward). The subject is then able to predict an outcome during the presentation of the stimulus (i.e., conditioned stimulus: CS). Furthermore,

the subject often needs to use acquired CS-reward (or no reward) relationships to facilitate subsequent adaptive behaviors. Previous studies have shown that neurons in the orbitofrontal cortex (OFC) develop firing in response to both CS and reward outcomes. OFC is hypothesized to be critical in inference based on acquired associative relationships between multiple CS and outcomes. However, precise roles of OFC in such inference and the contribution of specific subtypes of projection neurons are unknown.
To address these questions, food-restricted mice were trained to learn CS1-reward (a food pellet) and CS2-no reward associations in a blocked manner, and the stimulus-outcome relationships were then reversed. Conditioned responding (CR) was defined as the time in front of a food cup in anticipation of reward following CS presentation. Here we show that optogenetic inhibition of OFC at the time of omission of expected reward following CS1 in the reversal phase, using a red-light sensitive chloride pump Jaws expressed in all layers of OFC, delayed extinction of the CR during CS1. Notably, this inhibition also delayed subsequent CS2-reward association, despite no inhibition during the association. By contrast, optogenetic inhibition of Jaws-expressing superficial layers 2/3 of OFC at the time of omission of expected reward following CS1 induced an increase of CR during CS2. These distinct behavioral effects were not evident when new CS3 was introduced instead of CS2 or CS1, or the optogenetic inhibition was from the beginning of CS1. These results pinpoint temporally, context-, and layer- specific bidirectional causal roles of OFC in the derivation of inference of the relationship between specific CS and reward outcome, based on acquired associative relationships between multiple conditioned stimuli and reward outcomes.

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Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: H.01. Animal Cognition and Behavior

Support: R01-DA032758

Title: Establishing causal links between the orbitofrontal cortex and economic decisions

Authors: *S. N. BALLESTA[1,2], W. SHI[2], K. E. CONEN[2], C. PADOA-SCHIOPPA[2];
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Abstract: Multiple lines of evidence link economic choice behavior to the orbitofrontal cortex (OFC). Most notably, studies in which monkeys chose between different juices showed that neurons in OFC encode the identities and subjective values of offered and chosen goods. Furthermore, the population dynamics in OFC reflects an internal deliberation, and activity fluctuations in different groups of neurons correlate with choice variability. There results suggest that economic decisions are generated within this area. However, causal links between neural activity in OFC and economic choices have not yet been established. In principle, such links are demonstrated if electrical stimulation predictably biases choices. Building on this concept, classic work in area MT found that low-current stimulation facilitates, while high-current stimulation disrupts perceptual decisions. One challenge in applying this concept to economic choices is the lack of columnar organization in OFC. In other words, neurons associated with two goods available for choice are physically intermixed in cortex. To circumvent this challenge, we developed two experimental paradigms. In Exp.1, monkeys chose between two juices offered sequentially (pseudo-random order). High-current stimulation (≥100 μA) delivered during offer1 or during offer2 consistently biased choices against the juice offered during stimulation. Moreover, high-current stimulation during offer2 (when values were compared) increased choice variability (i.e., disrupted decisions). In Exp.2, we took advantage of the fact that *offer value* cells in OFC undergo range adaptation. Because of adaptation, for any given juice, the increase in offer value induced by low-current stimulation should be proportional to the value range. If two juices are offered, low-current stimulation should increase both values, but ultimately bias choices in favor of the juice with the larger value range. In the experiments, monkeys chose between two juices offered simultaneously, and we delivered electric current (50 μA). Confirming predictions, the stimulation induced a choice bias strongly correlated with the difference in value ranges. These results demonstrate that economic decisions are causally related to neural activity in OFC.

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Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.04/Z42

Topic: H.01. Animal Cognition and Behavior

Title: Stimulation of serotonergic terminals in the orbitofrontal and medial prefrontal cortices differentially affects waiting for the future rewards

Authors: K. W. MIYAZAKI[1], ***K. MIYAZAKI**[1], A. YAMANAKA[2], K. F. TANAKA[3], K. DOYA[1];

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Abstract: Optogenetic activation of serotonin neurons in the dorsal raphe nucleus (DRN) enhances patience in waiting for future rewards (Miyazaki et al., 2014) and the effect is maximized when the probability of reward delivery is high and the timing of delivery is uncertain (Miyazaki et al., 2018). Here we explored which serotonin neuron projecting areas contribute to these effect by optogenetic terminal stimulation in orbitofrontal cortex (OFC), medial prefrontal cortex (mPFC), and nucleus accumbens (NAc). Tph2-ChR2 transgenic Mice (n = 15) were trained to perform a sequential tone-food waiting task (Miyazaki et al., 2014, 2018) with two reward delay conditions with 75% reward probability: (i) fixed 6 s (D6 test, low timing uncertainty) and (ii) randomly set to 2, 6, or 10 s (D2-6-10 test, high timing uncertainty). Each mouse was implanted optic fibers into both the DRN and one of the serotonin projecting areas. In OFC-DRN group (n = 5), optogenetic stimulation of serotonergic terminals in the OFC during waiting for delayed rewards significantly increased waiting time in reward omission trials compared to that without optogenetic stimulation (D6 test, 11.97 ± 0.28 vs. 10.72 ± 0.30 s; D2-6-10 test, 16.67 ± 0.29 s, vs. 13.76 ± 0.30 s). In mPFC-DRN group (n = 5), the waiting time with serotonin activation in mPFC was significantly longer than without serotonin activation in D2-6-10 test but not in D6 test (D6 test, 11.16 ± 0.28 s vs. 11.02 ± 0.23 s; D2-6-10 test, 16.50 ± 0.43 s, vs. 14.75 ± 0.31 s). In NAc-DRN group (n = 5), there was no significant difference of waiting time with and without optogenetic stimulation in the NAc (D6 test, 10.97 ± 0.22 vs. 10.97 ± 0.24 s; D2-6-10 test, 14.08 ± 0.33 s, vs. 14.07 ± 0.38 s). In each group (n = 15), the waiting time with serotonin activation in the DRN was significantly longer than without serotonin activation (D6 test, 12.17 ± 0.14 s vs. 10.83 ± 0.11 s; D2-6-10 test, 18.92 ± 0.26 s, vs. 14.08 ± 0.18 s). In summary, serotonergic stimulation in the OFC promotes waiting similar as affectively as the DRN optogenetic stimulation, while serotonergic stimulation in the mPFC promotes waiting only when timing uncertainty of future rewards is high. These results suggest that serotonin in mPFC affects evaluation of time committed, while serotonin in OFC in responsible for overall evaluation of delayed reward.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Support: MEXT 17022052

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KAKENHI 25282246
KAKENHI 26119504
KAKENHI 26330266
KAKENHI 16H03301

Title: Causal role of monkey orbitofrontal cortex on reward value computation and decision-making

Authors: *T. SETOGAWA[1], T. MIZUHIKI[1], N. MATSUMOTO[2], B. J. RICHMOND[3], M. SHIDARA[1];
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Abstract: When we choose one item from several alternatives, we consider their values from amount of reward and the amount of work needed to obtain them. One of a candidate brain region related to such a reward value computation is orbitofrontal cortex (OFC). Here we studied whether 1) neurons in OFC are related to the value difference between offered options, and 2) there is a causal link between OFC and choice. We developed a decision-making schedule task and recorded single neuron activity from monkey OFC during this task. Two monkeys were initially trained to perform a reward schedule task. In this task, the monkey had to complete the schedule composed of 1, 2 or 4 trials of visual discriminations to earn 1, 2 or 4 drops of liquid reward. After learning this task, the decision-making schedule task was introduced. This task had a decision-making part and a reward schedule part. In the decision-making part, two choice targets (CT) were presented sequentially. Brightness and length of the CT were proportional to the amount of liquid reward (1, 2, or 4 drops) and the number of the visual-discrimination trials (1, 2, or 4 trials) needed to obtain reward, respectively. After both first and second CTs had been presented, the same two CTs simultaneously reappeared side by side of the fixation point. The monkey was required to choose one of the two CTs by touching the corresponding bar in the chair. Then, the chosen reward schedule task was started. We recorded 256 neurons in the monkey OFC (137 and 119 neurons from each monkey). The values of each CT were estimated from the monkey's choice behavior using an exponential discounting model. To analyze the relation between the firing rate in the second CT period and the presented CT values, we introduced seven analytic models and carried out a model selection by comparing AIC. 21.9% (56/256) of the neurons showed a significant correlation with value difference between two offered CTs. Inactivating a small regions of OFC rich in neurons coding for choice-related values using muscimol caused both slower to choose and more likely to choose the less valuable alternative, when the value difference was small. Thus, OFC neurons code for value information that could be used to guide choices, and these signals have a direct influence on the choice.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Title: Interaction between basal forebrain orbitofrontal cortex and secondary visual cortex during a visual discrimination task

Authors: *P. GOMBKOTO, P. VARSANYI, C. M. CHAVEZ, P. ZIOBRO, L. ZABORSZKY; Ctr. for Mol. and Behavioral Neurosci., Rutgers The State Univ. of New Jersey, Newark, NJ

Abstract: Basal forebrain (BF) cholinergic neurons provide the cerebral cortex with acetylcholine. Despite the long-established involvement of these cells in sensory processing, attention, and memory, the mechanisms by which cholinergic signaling regulates cognitive processes remains elusive. In a visual discrimination task, we examined cholinergic and non-cholinergic firing in basal forebrain (BF) which modulates cortico-cortical interaction between orbito frontal cortex (OFC) and secondary visual cortex (V2) (Gombkoto et al. 2019). Our overall goal was to understand how neural firing and detection of short timescale interactions of neuronal pairs correlate with behavioral epochs and how cholinergic and non-cholinergic neuronal activity in the BF influence cortico-cortical information processing. We hypothesized, that cholinergic activity increases during tasks that require cognitive flexibility (during reversal learning) versus well-trained tasks. In order to test this hypothesis, we introduced a touch-screen based task that contains visual feature recognition, discrimination based on the two distinct visual cues, and decision making in which the location of the reward delivery was associated to the visual cue. We found that unit firing responded heterogeneously to the visual cues, discrimination presentation, reward, or punishment, in the three brain regions indicating that these units code specific aspects of the task. Single unit activity from OFC coded outcome of expectation and error signal. In V2, single units responded to complex visual features which was associated with only one type of cue. BF neurons increased their firing at the initiation of correct choices and during reward but were inhibited during punishment when the animals were well trained. However, during reversal learning sessions, we found sustained activity by putative cholinergic cells specifically during correct trials but not incorrect trials. This sustained cholinergic activity may have influenced cortical processing allowing improved behavioral performance during reversal learning, since we did not observe this firing pattern when the animal was well trained. Our study defines how identified cholinergic and non-cholinergic firing in the BF modulate cortical network during learning.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Title: Distinct local and long-range cortical dynamics in an adaptive decision-making task

Authors: *A. BANERJEE, G. PARENTE, J. TEUTSCH, C. LEWIS, F. VOIGT, F. HELMCHEN;
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Abstract: Adaptive decision-making is a key component of flexible behavior, which enables animals to select appropriate goal-directed strategies based on the evaluation of recent stimulus/action-outcomes. The prefrontal areas of the mammalian neocortex, especially the orbitofrontal cortex (OFC), play an important role in invoking rule-based strategies to enable flexible learning. However, the neural circuit mechanisms in OFC and its interactions with different hierarchical cortical areas underlying such processes remain elusive. To study neural circuits of flexible decision-making, we developed a tactile-discrimination-based reversal learning task for head-fixed mice. We trained mice in a ‘Go/No-go’ texture discrimination task and then enforced them to relearn the task after a ‘Go/No-go’ rule-switch. Mice exhibited high performance during learning and re-learned the task upon reinforcer devaluation. Upon silencing lateral OFC, mice showed impaired reversal learning but intact acquisition of a new task-rule. To investigate how altered reward contingency is encoded and retrieved in distinct neuronal subpopulations in OFC, we employed 2-photon imaging through a rod-like GRIN lens to measure learning-induced changes in specific neural circuits. Longitudinal imaging of trial-by-trial Ca2+ responses from the same subsets of OFC neurons in mice expressing GCaMP6 in L2/3 neurons, revealed that OFC neurons are a key substrate assigning value to the sensory context. We also imaged neuronal responses in primary somatosensory cortex (S1). In S1, distinct neuronal subpopulations showed 'stimulus-selective' as well as ‘outcome-selective’ responses. The ‘outcome-selective’ neurons were differentially modulated by reward-history and altered response selectivity upon reversal. Silencing OFC-to-S1 projections following rule-switch impaired these plastic changes in S1 neurons. Taken together, our experiments shed light on the

circuit mechanisms underlying behavioural flexibility, indicating a crucial role of mouse OFC neurons in encoding predictive 'teaching signals' that drive adaptive changes in sensory cortices and in behavior.

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Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.08/AA4

Topic: H.01. Animal Cognition and Behavior

Support: NIH K08DA039351
Pew Biomedical Scholars Program
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: Decision-making in the context of multi-attribute options

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Abstract: Optimal decision-making often requires evaluating multiple attributes of available options. When deciding between two cars to purchase, one might take into account the vehicles' gas mileage, reliability, safety, and general aesthetics among other aspects, complicating the decision-making process. It is currently unclear how multiple attributes are instantiated in neural activity during a decision and how such attributes are combined into a general value signal and represented and evaluated separately in neural activity. The OFC is known to play a critical role in representing stimulus values, and may simultaneously or sequentially represent the overall value of the stimulus and the value of individual stimulus attributes. In order to better understand the mechanisms through which multi-attribute stimuli are represented in neural activity, we trained two monkeys on a choice task in which composite stimuli were predictive of both the probability of reward and the level of sweetness. A trial consisted of two options, each represented by two bars of differing colors indicating the probability and sweetness of the reward. In order to make a choice, subjects had to fixate on the option and release a touch sensitive bar. Both subjects formed clear preferences for options with higher probability of reward and higher sweetness. We found that the subjects' decisions were differentially influenced by each attribute, and that their decision-making strategies changed over the course of a session, with the probability attribute more predictive of choice at the beginning and sweetness becoming more predictive toward the end. We will record from the OFC using multi-contact

arrays to determine how complex stimuli are represented in neural activity, and how such neural representations may change as discrete attributes become more or less predictive of choice behavior.

Disclosures: **Z.S. Gillis:** None. **A.Q. Perkins:** None. **E.L. Rich:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: KAKENHI 16H02061, 19K06948 and 19H05028 to J.H.
Sir Henry Wellcome fellowship 106101 to A.L.
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Title: Orbitofrontal-to-striatal projection drives confidence-dependent choice bias

Authors: *J. HIROKAWA[1], A. LAK[2], T. OTT[3], T. OHNUKI[1], Y. OSAKO[1], H. MANABE[1], Y. SAKURAI[1], A. KEPECS[3];
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Abstract: In the face of environmental uncertainty adaptive behavior requires continuous changes in decision strategy. Theoretical considerations suggest that changes in choice strategy should reflect both decision outcome and confidence in obtaining the outcome. Orbitofrontal cortex (OFC) and striatum (STR) have been implicated in the computation of decision confidence and reward value, and their manipulation is known to produce choice biases. Therefore, we set out to examine the role of the OFC to striatum (OFC-STR) projecting neurons in shaping trial-by-trial choice strategy under perceptual uncertainty.
We designed a perceptual decision making task in which rats were encouraged to attend to the past outcomes of their choices. We trained rats in a 2-alternative odor-guided decision task, and varied perceptual uncertainty by changing the odor mixture ratio across trials. Rats received water reward after correct choices, while incorrect choices were not rewarded and led to a repeat of the stimulus in 50% of trials. We observed that their choices showed systematic biases depending on the outcome and difficulty of past choices. The influence of past outcomes on perceptual decisions was strongest when the previous sensory stimulus was difficult to judge, and thus the confidence in obtaining the reward was low. This choice bias was explained by reinforcement learning models that incorporate decision confidence into their teaching signals and hence adjust learning according to decision confidence (Lak et al, 2017).
Next, we monitored the activity of OFC-STR projecting neurons during the task. To target OFC-

STR neurons, we used a retrograde viral strategy to express ChR2 and optogenetically identify them based on short-latency spikes to brief light pulses delivered through a fiber next to the recording tetrodes. We found that 23/24 of OFC-STR neurons significantly encoded the outcome of the trial with sustained activity extending beyond the feedback period and until the next trial. To evaluate the behavioral function of OFC-STR neurons, we optogenetically activated or suppressed them using ChR2 or Jaws. Optogenetic activation (1s, 10Hz) during the outcome period increased choice bias in the following trial whereas optogenetic suppression (10s, continuous) had the opposite effect, reducing the choice bias. These behavioral effects can be mimicked in our model by manipulating the post-decision decision value, the reward expectation associated with a perceptually ambiguous decision (Lak et al, 2017). These results reveal that the OFC-STR pathway is important for signaling the decision value, and hence for regulating confidence-dependent choice biases.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: K08 DA039351
Pew Biomedical Scholars Program
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation

Title: The role of the orbitofrontal cortex in updating value expectations

Authors: *E. L. RICH[1], Z. S. GILLIS[2];
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Abstract: Expectations inform decision-making and can alter our perceptions. Aberrant expectations are a feature of psychiatric disorders, such as major depressive disorder, yet the neural mechanisms through which expectations are formed, maintained, and overridden are still unclear. The OFC is known to encode the value of reward-predictive stimuli, and distinct regions of OFC may serve disparate roles in updating stimulus-value associations. To understand the neural mechanisms through which expectations are instantiated and updated, we trained two monkeys on a reward expectation task in which pictures served as stimuli predicting rewards with varying levels of sweetness and bitterness. During forced choice trials, only one reward-predictive stimulus was offered. During free choice trials, the subject was presented with two

options, and chose between them. To receive an initial reward, the subject fixated on a stimulus and simultaneously released a touch sensitive bar. Initial reward delivery was followed by a 4 second response interval, during which the subject could freely tap the bar for small amounts of additional reward. Both subjects formed clear and stable reward preferences, selecting sweeter or less bitter rewards on free-choice trials. During the response interval, subjects tapped the bar more frequently for more preferred rewards, providing a time-varying behavioral measure of motivation to earn each reward. To determine whether bar tapping was motivated by expectations or actual rewards received, mismatch trials were included in which the reward delivered was not the expected reward. We found that subjects were initially motivated by expectations, and gradually adjusted their response rates, so behavior was better predicted by the actual rewards. Additionally, we found that subjects adapted their tapping behavior based on the mean and variance of available reward sweetness levels within an individual session. Preliminary neural data from OFC show modulation of beta frequencies that changes with expectation updating on mismatch trials. Using multi-contact arrays we will record simultaneously from OFC and gustatory cortex to determine how expected values and taste perception dynamically motivate behavior.

Disclosures: E.L. Rich: None. **Z.S. Gillis:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: Wellcome Grant WT 095495
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Title: Activity of single neurons in the macaque orbitofrontal cortex complies with the continuity axiom of expected utility theory

Authors: *S. FERRARI-TONIOLO, W. SCHULTZ;
Univ. of Cambridge, Cambridge, United Kingdom

Abstract: A possible mechanism for decision making under risk involves the computation and comparison of the subjective values (SV) of all available options. Expected utility theory (EUT) was the first rigorous axiomatic theory able to describe choices in this framework. The continuity axiom of EUT demonstrates the possibility of representing SV on a finite, numerical scale. We tested the continuity axiom in monkeys to verify that their choice behavior could be described in terms of numerical SV, a necessary step for comparison with the inherently cardinal neuronal

responses. Two rhesus monkeys were trained to choose between gambles with different reward magnitude-probability combinations. The continuity axiom was tested by verifying the existence of choice indifference between a certain reward and a gamble with a specific probability. Behavioral results (presented at the 2017 SfN meeting) confirmed the compliance with the continuity axiom. We recorded the activity of single orbitofrontal neurons while monkeys were presented with the same gambles used in the continuity tests. The activity of neurons coding the numerical SV predicted by EUT should be consistent with the pattern of choice indifferences observed in the continuity tests: the responses of such neurons should be modulated by the reward probability and be equal at the indifference point. We found that different classes of neurons were differently modulated by combinations of reward magnitude and probability. A first group of neurons was modulated by both magnitude and probability, a general necessary requirement for value coding. A subset of these neurons responded according to the continuity axiom, a more stringent condition for the coding of numerical SV. Two further neuronal classes were found to encode only the reward magnitude or the reward probability, while another group responded differentially to the presentation of probabilistic or certain rewards. These activity classes are compatible with the mechanism for computing SV delineated by EUT: different computational units could encode the subjective weight assigned to magnitudes (utility) and to probabilities (probability weighting), and these "partial" values could be combined into the signal observed in neurons complying with the continuity axiom. These neurons would represent the final step in encoding the SV, making them suitable candidates for driving (subjectively) optimal decisions.

Disclosures: **S. Ferrari-Toniolo:** None. **W. Schultz:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Title: Structured representations in orbitofrontal neurons during time investment decisions

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Abstract: Every decision we make is accompanied by a sense of confidence about its likely outcome. This sense informs subsequent behavior, such as investing more ―whether time, effort, or money― when reward is more certain. We previously showed that using decision confidence to guide time investment relies on the orbitofrontal cortex (OFC) in rats. However, it is unknown how the activity of OFC neurons supports confidence-guided time investment behavior. Here we show that the activity of OFC neurons is highly structured: distinct groups of neurons show unique temporal response profiles and represent distinct task variables that enable confidence-guided time investment. We trained rats to make choices based on evidence from two different sensory modalities (auditory clicks or olfactory mixtures). After making a choice, rats had to wait in a choice port to obtain an uncertain, randomly delayed reward. The time rats were willing to invest in waiting for a potential reward reflected their decision confidence. We found that individual OFC neurons showed rich and complex response patterns; different neurons were active during different task epochs and encoded different aspects of the task, such as choice, decision confidence, or elapsed time. However, these dynamic activity patterns were not randomly distributed but clustered into a small set of typical response profiles that spanned the entire duration of a trial. Many neurons encoded decision confidence immediately after making a choice, irrespective of the sensory modality used to make a choice. Another group of neurons showed ramping activity during the time investment period, predicting the rats' time investment, while different neurons sharply increased their activity just before leaving decisions. OFC thus links information about decision confidence with subsequent time investment behavior and leaving decisions and could thereby mediate confidence-guided economic decisions.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Support: NIH R01 MH109484

Title: Interactions between the medial orbitofrontal cortex and nucleus accumbens facilitate risk assessment behaviors

Authors: *M. K. LOH, N. C. FERRARA, J. A. ROSENKRANZ;
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Abstract: The ability to assess risk and predict potential negative consequences heavily biases the decision-making process and is evolutionarily important for survival. The nucleus accumbens (NAc) supports reward-directed actions and its activity is reflective of risky behavior. These

behaviors are influenced by input from several brain regions to the NAc. Namely, the medial orbitofrontal cortex (MO) contributes to behavior guided by reward probability and sends direct projections to the NAc, suggesting that MO-NAc efferents may permit risk evaluation. Therefore, a clearer understanding of MO-NAc interactions is crucial to elucidate the neural mechanisms underlying risk assessment. Here, we investigated MO-NAc interactions in gating risk assessment behaviors. Using a disconnection approach, we found that MO-NAc interactions may be necessary for risk assessment behaviors in rats, observed as stretch and attend postures (SAP) on the elevated plus maze (EPM). In line with these findings, we found that adolescent subjects, who characteristically have delayed frontal lobe maturation and potentially less cortical input influence, also exhibited less EPM risk assessment behaviors than adults. A balance between reward versus risk elements is weighed during decision-making, perhaps reflected by the interactive nature of cortical and limbic inputs into the NAc. Therefore, we investigated if MO-NAc interactions influence circuits that underlie reward-seeking. Using *in vivo* extracellular single-unit electrophysiology, we isolated NAc neurons responsive to basolateral amygdala (BLA) stimulation, as BLA-NAc projections facilitate reward-seeking behaviors and attenuate cortical-NAc interactions. We hypothesized that MO stimulation will diminish BLA-evoked NAc spiking. Single pulses at increasing interstimulus intervals and frequency-varying trains were delivered to the MO to assess its effects on BLA-evoked NAc spiking. We found that MO single-pulse stimulation enhanced BLA-evoked NAc spiking in a time-dependent manner, optimal at the 11-ms ISI. Shifts to BLA-evoked NAc spike probability by MO train stimulation were also frequency-dependent. Further, MO train stimulations resulted in a bimodal distribution of NAc activity; half of BLA-evoked NAc neurons showed diminished spike probability to MO train stimulation while the remainder showed an increase. This suggests that MO activity timing and frequency are important NAc activity modulators. Due to the behavioral role of MO and BLA-NAc projections, these interactions may contribute to the neurobiological mechanism in the incorporation of risk information to influence reward-directed actions.

Disclosures: **M.K. Loh:** None. **N.C. Ferrara:** None. **J.A. Rosenkranz:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: Army Research Office W911NF-16-1-0474
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Title: Distinct roles of the pACC and cOFC in cost-benefit decision-making

Authors: *G. K. PAPAGEORGIOU[1], K.-I. AMEMORI[3], H. N. SCHWERDT[1], D. J. GIBSON[2], A. M. GRAYBIEL[1];
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Abstract: The pregenual anterior cingulate cortex (pACC) has been implicated in learning, decision-making and mood-related disorders, but very little is known about a relatively adjacent region, the caudal parts of the orbitofrontal cortex (cOFC). Although the orbitofrontal cortex (OFC) has been actively investigated, surprisingly, most electrophysiological OFC studies have focused on more rostro-medial or lateral parts of this region. Therefore there is overall uncertainty about the role of the more caudal parts of the OFC in decision-making and learning processes. Here we concurrently investigated the role of each brain region during a cost-benefit approach-avoidance (Ap-Av) task, a task well-established for use in non-human primates and humans. We have trained two adult macaque monkeys (one male, one female) on a visually guided Ap-Av task. During the task, monkeys had to look and fixate at targets displayed on a screen to choose offers comprising of certain amounts of reward (water or juice) and punishment (airpuff), signaled by the length of red and yellow bars, respectively. For the purpose of electrophysiological monitoring during the task performance, moveable platinum-iridium electrodes were chronically and bilaterally implanted in the pACC and the cOFC. In addition, physiological parameters including pupil diameter, licking and pulse oximetry were recorded for estimate the behavioral states. Both animals exhibited a stable decision boundary between Ap and Av choices during the experiment, often accepting an offer when a reward was higher than punishment and rejecting it when the punishment was greater than reward. A further analysis of the neural data revealed differential firing during the various task events in pACC and cOFC. Specifically, neurons in the pACC exhibited higher firing rates during the presentation of the compound offer, whereas neurons in the cOFC were more active during the outcome delivery period, especially during the delivery of the negative outcome (i.e., airpuff). These results show that both of these regions play a significant role during cost-benefit decision-making but that they may influence differentially the decision-making process.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: R01 DA047870

Title: Effect of orbitofrontal cortex DREADDs inhibition on probabilistic discrimination reversal learning and win-stay, lose-shift strategies in male and female rats

Authors: *S. KOLLI[1], C. G. AGUIRRE[1], E. NGUYEN[1], A. STOLYAROVA[1], M. SPITMAAN[2], A. SOLTANI[2], A. IZQUIERDO[1];
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Abstract: The orbitofrontal cortex (OFC) supports functions related to reward learning and decision making and exhibits functional heterogeneity, even in rats (Izquierdo, 2017). Most sectors of rat OFC have been shown to support reversal learning, but less is known about its role in supporting learning under different schedules of reinforcement during probabilistic reversal learning (PRL). For most PRL studies, OFC has also mostly been manipulated using classic techniques like pharmacological inactivations and lesions, with past work predominantly reporting effects only in male rodents. Here we tested both male (n=8) and female Long-Evans rats (n=8) on PRL following expression of inhibitory hM4Di DREADDs on a CaMKIIα promoter in ventrolateral OFC and compared them to rats receiving eGFP null virus, or systemic vehicle injections to control for behavioral effects of virus exposure or hM4Di ligand, clozapine-n-oxide (CNO). After discrimination, rats were injected with either CNO (3.0 mg/kg s.c.) or vehicle daily, prior to testing on PRL via touchscreen response where they could select between two visual stimuli, assigned as the Better (B) or Worse (W) options, rewarded with probability pR(B)=0.90 or pR(W)=0.10, respectively. The control groups were not significantly different, so their data were collapsed. Analyses were focused on the first 10 sessions of each phase for mean probability correct, initiation omissions, and the number of no rewards per session. A repeated-measures ANOVA revealed no main effect of sex or treatment group differences, or sex x treatment group interaction for these measures on initial discrimination learning, when rats initially learned probabilities of reward. There was, however, a significant session x active virus group interaction for probability correct during PRL, with the most pronounced deficits in early PRL following OFC inhibition. Rats could either select the same stimulus after a reward (i.e. Win-Stay) or switch to a different stimulus following a loss (i.e. Lose-shift). Trial-by-trial analyses were conducted to assess win-stay/lose-shift strategies during early learning. Following OFC inhibition, rats adopted significantly more of a win-stay strategy and less of a lose-shift strategy. Also following OFC inhibition, rats were more likely to choose the same stimulus on the subsequent trial, regardless of the outcome. Collectively, the data suggest reduced negative but enhanced positive feedback sensitivity, and enhanced perseverative choice behavior following OFC inhibition. Ongoing work is aimed at comparing learning under other probability schedules, and probing more precise timing of OFC involvement in PRL.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: R37MH058883-23
P50MH106435-04

Title: Overtraining of avoidance in rodents as a model for OCD-like compulsions

Authors: *C. I. HUERTAS PÉREZ, Jr.[1], F. J. MARTINEZ-RIVERA[3], M. J. SANCHEZ-NAVARRO[3], J. E. PEREZ-TORRES[3], *G. J. QUIRK[2];
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Abstract: Obsessive-compulsive disorder (OCD) is characterized by a persistent urge to avoid perceived threats in the absence of danger. It can be treated with exposure-with-response-prevention (ERP) therapy, in which patients are prevented from carrying out compulsions in response to triggers. We previously used platform-mediated active avoidance to model ERP (Rodriguez-Romaguera et al., 2016), but we now examine overtraining of avoidance to capture the long-term negative reinforcement feature of compulsive behaviors. Food-deprived rats were conditioned for either 8 days or 20 days (9 trials per day) to step onto a platform to avoid a tone-signaled footshock. Mounting the platform prevented access to a bar that delivered sucrose pellets. Following conditioning, rats underwent 4 days of extinction with response prevention training (Ext-RP), where tones were presented without shocks in the presence of a barrier blocking access to the platform. This was followed by a single test session where the tone was presented with the barrier removed. Rats in 8d and 20d groups showed equivalent avoidance conditioning, but 20d rats were severely impaired in extinction of freezing during Ext-RP. When the barrier was removed, 20d rats spent significantly more tone-time on the platform ($p<0.001$), with 75% showing persistent avoidance compared to 37% in the 8d group. 20d rats also displayed heightened anxiety in an elevated plus maze (open arm time (s): 8d: 72.3±14.3; 20d: 32.9±8.5). cFos analysis revealed that the minority of rats exhibiting persistent avoidance in the 8d group had elevated activity in the expected avoidance structures (prelimbic (PL) cortex, nucleus accumbens). However, 20d rats exhibiting persistent avoidance did not have elevated activity in these structures. Instead, the minority of 20d rats not exhibiting persistent avoidance showed elevated activity in lateral orbital/insular cortex, dorsolateral striatum and paraventricular thalamus. Thus, overtraining induced a pre-potent avoidance response not driven by the known avoidance circuit. We next attempted to reverse the effects of overtraining by

lengthening Ext-RP from 4 to 10 days. Preliminary data indicates that the 20d rats given 10d of Ext-RP training continued to show elevated avoidance when the barrier was removed. Furthermore, cFos was not elevated in PL, resembling the impaired pattern of overtraining followed by 4 days of Ext-RP. Taken together, our results suggest that prolonged expression of avoidance-type compulsions alters neural circuits and drives pre-potent responses that may be resistant to extinction based therapies.

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Poster

514. Decision Making: Orbitofrontal Cortex

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Support: Max Planck Society
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Title: An automated arena for *in vivo* recordings of freely behaving lizards

Authors: *S. WEISS, G. J. LAURENT;
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Abstract: Reptiles occupy a critical limb of the evolutionary neuro-developmental tree, sharing a layered cortical architecture with mammals and a dorsal-ventricular ridge (DVR) with birds (or avian reptiles). Recent studies of the reptilian brain in this laboratory have focused on electrophysiological recordings from brain slices, ex vivo brain-explants or anaesthetized animals (Fournier et al., 2018), and on single cell transcriptomics approaches (Tosches et al., 2018). Data collected in vivo are rare, with the exception of sleep-related brain activity in lizards (Shein-Idelson et al., 2016). While behavioral studies have established learning abilities in several lizard species, current tests of lizard cognition lack standardized testing methods and provide no data on brain activity during behavioral tasks. It is thus difficult to generalize results across lizard species or between reptiles and other amniotes. In the current study we developed and used an automated test arena, inspired by the design of a “plus-maze” commonly used to induce different behavioral strategies in rodents. Bearded dragon lizards (Pogona vitticeps) were trained to perform behavioral tasks in the arena, while local filed potential (LFP) and single-unit data were recorded from dorsomedial cortex (a molecular homolog of the CA fields in mammalian hippocampus) and DVR (a homolog, among others, of parts of the mammalian amygdala). We hope that this research can help standardize behavioral neuroscience research in

reptiles and enables a comparative analysis of brain activity across mammals, birds and reptiles, in order to characterize the core and shared anatomical and functional features of memory systems in amniotes.

Disclosures: S. Weiss: None. **G.J. Laurent:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Title: Neurons in the orbitofrontal cortex encode the same decision variables in different choice tasks

Authors: *W. SHI[1], S. BALLESTA[2,1], C. PADOA-SCHIOPPA[1];
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Abstract: Economic choices involve two mental stages - values are assigned to the available options and a decision is made by comparing values. Experiments where monkeys chose between two juices have identified different groups of cells in the orbitofrontal cortex (OFC) encoding the value of individual options (*offer value*), the binary choice outcome (*chosen juice*) and the *chosen value*. These variables capture both the input and the output of the choice process, suggesting that these groups of neurons constitute the building blocks of a decision circuit. This and other results provide a basic understanding for the neural underpinnings of economic decisions. However, current notions emerged mostly from studies where two offers were presented simultaneously. Other authors suggested that decisions under sequential offers might rely on different mechanisms. In a recent study, we examined economic choices under sequential offers (Ballesta & Padoa-Schioppa, *biorxiv*). Individual neurons in OFC encoded different variables in different times windows. However, an analysis across time windows still revealed three groups of neurons: *group1* cells encoded the value of one particular juice whenever that juice was offered; *group2* cells encoded in a binary way the juice type present on the monitor and, subsequently, the chosen juice; *group3* cells encoded the value of the juice currently offered and, subsequently, the chosen value. In the present study, we directly examined the relation between the cell groups identified under sequential offers and those identified under simultaneous offers.
In each session, a monkey chose between two juices offered in variable amounts. Trials with the

two choice tasks- simultaneous or sequential - were pseudo-randomly interleaved. We recorded the activity of 702 cells in OFC. Trials with the two choice tasks were analyzed separately. Thus each cell was classified for its activity under simultaneous offers and under sequential offers. In most cases, neurons tuned in either choice task were tuned in both choice tasks. Furthermore, at population level, an analysis of the contingency table of cell groups revealed a close correspondence between the two classifications. Specifically, [*group1*, *group2*, *group3*] closely corresponded to [*offer value*, *chosen juice*, *chosen value*] ($p<0.01$, Fisher's exact test). These results support the hypothesis that economic decisions under simultaneous and under sequential offers are generated in the same neural circuit, rather than based on two different mechanisms.

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Poster

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Topic: H.01. Animal Cognition and Behavior

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Title: Contrasting neural representations in the orbitofrontal cortex under single and multi-attribute decisions

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Abstract: Combining evidence from lesions, imaging, modeling and neurophysiology, previous results established a clear link between economic choice and subjective values represented in the OFC. Subjective value computation implies a trade-off among multiple attributes and it has been proposed that the central OFC (areas 13m/l and 11l) makes a unique contribution to economic decisions by computing subjective values through integrating multiple attributes of goods. An outstanding question that follows is whether central OFC is dedicated to multi-attribute economic decisions or subserves reward-based decisions in general. Here, we sought to investigate this question by training monkeys to perform alternately in a multi-attribute choice (MAC) and a single-attribute choice (SAC) task. In the MAC task, the animal chose between two

juices of variable amounts while in the SAC task, the animal chose between the *same* juice of different amounts. In the the MAC task, two offers were represented by two sets of symbols in different color displayed to the left and right of the central fixation point. In the SAC task, the two sets of symbols have the same color, indicating the same juice of different quantity. Behaviorally, the animal showed typical trade-off between juice quantity and taste in the MAC task and always chose the offer of larger quantity in the SAC task. In each recording session, we simultaneously recorded an ensemble of neurons (10 on average) under both tasks. We achieved stable recordings from over 200 neurons across two tasks from one animal. We hypothesized that if OFC subserves reward-based decisions in general, when the animal transitions from the MAC to the SAC task, OFC neurons would adapt to the decision context by switching from representing the decision process in juice-based reference frame to that in spatial reference frame. However, we discovered that 1) There are significantly more task-related neurons in the MAC task than that in the SAC task. 2) In the MAC task, OFC neurons primarily encode task-related variables associated with the choice process in a good-based representation, including offer value, chosen value and chosen juice, while In the SAC task, the same population of neurons primarily encode chosen quantity only. 3) In the MAC task, a substantial proportion of neurons encode chosen juice while few neurons in the SAC task encode chosen side (choice outcome in spatial reference frame). These preliminary results based the regression analysis of single unit activity suggest that central OFC subserves the multi-attribute decision in good-based reference but not single-attribute decision in spatial reference frame.

Disclosures: X. Cai: None. **C. Xu:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.20/AA16

Topic: H.01. Animal Cognition and Behavior

Support: NIDA K99-DA036561

Title: Neural correlates of absolute and relative predictive validity in lateral orbitofrontal cortex during learning

Authors: S. VOLZ[1], M. KANG[1,2], I. REVERTE[1], F. ALHAZMI[1,2], M. IORDANOVA[3], ***G. ESBER**[1,2];
[1]Psychology, Brooklyn College, City Univ. of New York, New York, NY; [2]The Grad. Center, City Univ. of New York, New York, NY; [3]Concordia Univ., Montreal, QC, Canada

Abstract: A vast behavioral literature shows that the value of reward-predictive cues is not merely a function of how well they predict reward by themselves, but by comparison with other

cues, suggesting predictive validity is set in relative rather than absolute terms. This is evident in cue-competition phenomena, in which the presence of other predictors can curtail or drain the value that a cue would otherwise acquire given its statistical correlation with reward, or *absolute validity*. These phenomena are problematic for early models that viewed learning as being driven by a *local* prediction error (PE), or difference between the reward observed and the reward predicted by the cue, since those models predict that each cue will acquire value in proportion to its absolute validity. Instead, they fostered the prevailing notion that learning is driven by a common or *global* PE—the difference between the reward observed and a pooled or aggregate reward prediction based on all cues present. Models that subscribe to the latter notion view cues as competing for value during learning, such that only those that have high *relative validity* will ultimately acquire substantial value. Critically, despite the explanatory power of global PEs, emerging evidence indicates that local PEs also play a role in learning, and that the extent to which they do so is subject to individual differences. This suggests the existence of a learning-style axis, at one end of which individuals track the absolute validity of cues, while at the other end they track the cues' relative validity. To investigate the neural bases of the absolute-relative validity axis, we developed a novel cue-competition task in rats which is first to set absolute and relative validity in conflict, thus affording the starkest possible contrast between both learning styles and their neural underpinnings. Using this task, we recorded single-unit activity in the lateral orbitofrontal cortex (lOFC), a brain region known to encode the reward-signaling properties of cues. Interestingly, our results suggest that lOFC neurons track both the absolute and relative validity of cues, with a greater proportion of neurons representing the latter.

Disclosures: S. Volz: None. **M. Kang:** None. **I. Reverte:** None. **F. Alhazmi:** None. **M. Iordanova:** None. **G. Esber:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.21/AA17

Topic: H.01. Animal Cognition and Behavior

Support: Faculty Research Grant, University of Memphis (NWS)

Title: Optimization of a risky decision-making task for electrophysiology in male and female rats

Authors: *D. B. K. GABRIEL[1], A. E. LILEY[2], W. B. CAUGHRON[1], N. W. SIMON[1]; [2]Psychology, [1]Univ. of Memphis, Memphis, TN

Abstract: Risky decision-making is characterized by reward-seeking despite the possibility of punishment. The rat risky decision-making task (RDT) measures this behavior by presenting a

choice between a small, safe reward (one pellet) and a large reward (three pellets) accompanied by the risk of an increasingly likely punishing foot shock (Simon et al., 2009, Neuropsychopharmacology). Understanding the neurobiological mechanisms that drive risky decision-making is necessary for the development of interventions for disorders characterized by excessive risk-taking. Single unit electrophysiology allows synchronization of functional neuronal activity with behavior at exquisite temporal resolution, and is thus ideally suited to determine how neurons encode specific salient events during risky decision-making. Here, we developed an optimized, electrophysiology compatible version of the RDT for use in male and female rats. The RDT was altered to include only two risk blocks (0% and 50% risk of foot shock), with 8 forced choice (only one option available) and 40 free choice trials (both options available) in each block. To parse apart distinct epochs of the decision-making process, rats were trained to perform one-second sustained nose pokes into a lit trough 1) prior to each choice, and 2) prior to each outcome. While male rats were able to acquire these contingencies, females were inconsistent in ability to achieve trial criterion even after extensive training. Accordingly, the task was altered to include only the pre-decision nose poke hold, with outcomes delivered .5 seconds after reward choice. Both male and female rats acquired this iteration of the task, and demonstrated a comparable shift away from the large reward in the second block (50% risk of punishment). This task will facilitate ongoing investigation of the functional neuronal activity underlying individual differences in risk-taking across both males and females. Subjects are currently being implanted with microwire arrays for single unit recording in the orbitofrontal cortex, a brain region shown to contribute to risk-based decision-making.

Disclosures: D.B.K. Gabriel: None. **A.E. Liley:** None. **W.B. Caughron:** None. **N.W. Simon:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.22/AA18

Topic: H.01. Animal Cognition and Behavior

Support: NIDA K99-DA036561

Title: A computational model for the modulation of learning by the common and separate prediction error

Authors: *F. ALHAZMI[1,2], A. KRISHNAN[1,2], G. R. ESBER[1,2];
[1]Brooklyn College, City Univ. of New York, Brooklyn, NY; [2]The Grad. Center, City Univ. of New York, New York, NY

Abstract: Prediction error (PE) is a fundamental concept in associative and reinforcement-learning models, where it is viewed as the signal that drives learning. Current mainstream models assume that cues concurrently presented share a common PE, or difference between the observed and expected outcome, by virtue of which they compete for learning. However, mounting behavioral evidence from both rat and human studies suggests that learning is also modulated by a separate PE signal, or difference between the observed outcome and that expected on the basis of each cue considered in isolation, in keeping with earlier learning models. Crucially, how the two types of PE combine to modulate learning is not yet understood. Here, we aim to provide a computational account of PE integration specifically aimed at capturing the results of experiments attempting to disentangle the contribution of separate PE and common PEs to learning. Succinctly, our solution consists of combining separate and common PEs in a weighted sum fashion. In this Weighted Sum Model (WSM), the relative weight of each type of PE gives rise to learning-style continuum, at one end of which learning relies on common PEs while at the other end learning relies on separate PEs. This theoretical account explains widely reported individual differences in cue competition as well as variability across cues in their susceptibility to engage in cue competition. Performance and unique prediction of WSM are discussed in the context of other potential PE-integration mechanisms.

Disclosures: F. Alhazmi: None. **A. Krishnan:** None. **G.R. Esber:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

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Topic: H.01. Animal Cognition and Behavior

Support: Science and Technology Commission of Shanghai Municipality Grant No. 14JC1404900, 15JC1400104, 16JC1400101
Shanghai Municipal Science and Technology Major Project, Grant No. 2018SHZDZX05
National Natural Science Foundation of China Grant No. 31571102, 91632106

Title: Prefrontal mechanisms of economic decisions with sequential offers

Authors: *K. NI[1], Y. LIU[1], X. CAI[1,2];
[1]NYU-ECNU Inst. of Brain and Cognitive Sci., NYU Shanghai, Shanghai, China; [2]Shanghai Key Lab. of Brain Functional Genomics (Ministry of Education), Sch. of Psychology, East China Normal Univ., Shanghai, China

Abstract: A majority of studies in value-based decisions focus on decisions based on an available menu. However, in many real-life decisions, offers appear sequentially. Early studies

discovered that neurons in the OFC encode the value of offers available for choice. However, such studies failed to identify persistent value selective activity in the OFC. Therefore, it is unknown whether and how OFC supports economic choice of sequential offers. Anatomically, central OFC is interconnected with the lateral prefrontal cortex, which has pervasively been demonstrated to encode working memory through sustained activity. In current study, we sought to investigate how the prefrontal network may process value information in working memory for choice. To this end, we developed an economic choice task with sequential offer presentations. In the experiments, the animal chose between two juices offered in variable amounts. The animal maintained center fixation while two offers were presented sequentially on the left or right side. For each pair combination of juice quantities, the sequential order and the left/right configuration of offers were pseudorandomized and counterbalanced within each trial block. Terms "offer1" and "offer2" refer to the first and second offer appearing sequentially. In each trial, offer1 appeared for 500 ms followed by a delay of 1000 ms, after which offer2 appeared for 500 ms, then two saccade targets appeared on each side of the fixation point, and the monkey indicated its choice with a saccade. The combinations of the two offers were designed such that the animal had to wait for offer2 before making a decision. We recorded the activity of multiple prefrontal regions, including the central region of the orbitofrontal cortex (area 11 and 13) and the dorsal and ventral bank of the principal sulcus (LPFCd and LPFCv). We analyzed the activity of around 200 neurons in each of the 3 areas. The task design allowed the representation of goods and values in multiple reference frames (i.e., juice-based, order-based and (left/right) space-based reference frames). We examined neural representations of decision-related variables in all three reference frames in OFC, LPFCd and LPFCv. We discovered that when offer1 or offer2 was on, neurons in the OFC and LPFCv encode the value of the offers in multiple reference frames, however, representations of offer1 value did not persist throughout the delay period. Furthermore, binary choice signals emerge in order-based reference frame first, followed by those in space-based and juice-based reference frames. These activity patterns might reflect the decision through coordinated neural processes in multiple reference frames.

Disclosures: **K. Ni:** None. **Y. Liu:** None. **X. Cai:** None.

Poster

514. Decision Making: Orbitofrontal Cortex

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 514.24/AA20

Topic: H.01. Animal Cognition and Behavior

Title: Sex differences in the discounting of delayed punishment

Authors: *A. E. LILEY, D. B. GABRIEL, M. E. UDELL, H. J. SABLE, N. W. SIMON; Psychology, Univ. of Memphis, Memphis, TN

Abstract: Sex differences in sensitivity to punishment during decision-making have been observed in both humans and animal models. However, these studies are limited to designs in which punishment occurs immediately after a decision. To model consequences that occur later in time, we developed the Delayed Punishment Decision-making Task (DPDT). In this task, rats increased choice of rewards associated with punishment (shock) as delay preceding the punishment lengthened, demonstrating that subjects underestimate the negative value of delayed consequences. Males and females showed comparable avoidance of a large, punished reward when punishment occurred immediately. However, when delay was added between the reward and punishment, males showed a greater preference for this outcome than females. This indicates that females discount delayed punishment less than males. Estrous samples were collected from female rats via vaginal lavage, viewed under light microscope, and categorized by the presence of cornified epithelial cells, nucleated epithelial cells, or leukocytes. The four stages of the estrous cycle (proestrus, estrus, metestrus, and diestrus) were then compared to behavioral performance during the task. There were no significant changes in behavior during any stage of estrous during DPDT. Addition of a cue light bridging the delay between the reward and punishment produced a decrease in selection of rewards associated with delayed consequences that was not influenced by sex. Finally, neither male nor female rats demonstrated a correlation between DPDT and delay discounting, which measures preference for delayed rewards.
A region that likely plays a regulatory role in sensitivity to delayed punishment is the orbitofrontal cortex (OFC). We are currently implanting bilateral cannulae into the orbitofrontal cortex of male and female Long Evans rats to measure effects of OFC inactivation on sensitivity to delayed-punishment during DPDT. Ongoing studies will provide insight as to how the OFC affects the undervaluation of delayed consequences, and how this differs between males and females. Collectively, these experiments demonstrate novel sex differences in an understudied form of addiction-relevant punishment-based decision-making.

Disclosures: A.E. Liley: None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.01/AA21

Topic: H.01. Animal Cognition and Behavior

Title: Effects of a high fat diet on working memory and metabolism in rats

Authors: *H. M. MURPHY, C. H. WIDEMAN;
Neurosci., John Carroll Univ., University Heights, OH

Abstract: The nutritional status of an organism is paramount to optimal brain function. Research has provided evidence that chronic ingestion of a high fat diet is associated with cognitive

decline. The current study evaluated the effects that a high fat diet has on working memory and metabolism of rats. It was hypothesized that, compared to controls, a high fat group would display negative effects in both variables. The T-maze was used to assess working memory. A moveable door was employed to prevent access to one arm during forced (access to only one arm) runs. Rats were shaped for one week. At the beginning of the dark cycle on the first and second days, 250 µL of condensed milk, in a small glass container, was placed in each cage to familiarize the rat to the "treat" incentive. On day 3, 250 µL of treat was put at the beginning of the T-maze and the rat was placed into the maze to find it. For succeeding days, the treat was gradually restricted to the arms of the maze. Following the shaping period, habituation began on week 2 and continued for seven days. Every day during week 2, all rats were individually placed into the maze to complete both a forced run and a choice run. The forced run directed the rat down one of the arms with the incentive of the treat at the end, while the other arm was blocked. Time taken to find the treat was recorded. For the choice run, the rat was placed onto the stem of the T-maze and the block on the other arm as well as the treat were removed. The rat was then allowed to run down the stem and freely choose one of the arms. If the rat entered the same arm as the forced run, a correct response was recorded. If the opposite arm was chosen, an incorrect response was recorded and the rat was returned to its cage. Responses were recorded when the rat moved more than 10 cm down one arm. Forced runs lasted for 2 min, or until the rat found the treat. Choice runs lasted 2 min, or until the rat entered an arm. Body weight, food intake and water intake were recorded daily. Following habituation, each rat was randomly assigned to either the standard rat diet used during habituation or a high fat diet D12492 (Research Diets, Inc., New Brunswick, NJ). The experimental period lasted for 3 weeks and the paradigm utilized in habituation was employed. At the conclusion of the experimental period, rats were sacrificed and blood glucose and adiposity were determined. Working memory was significantly impaired in the high fat group, characterized by a 60% decrease in retention. Furthermore, there were marked increases in body weight, caloric intake, blood glucose, and adiposity in the high fat group. This study provides evidence that a high fat diet has a deleterious effect on working memory and negatively affects some metabolic processes.

Disclosures: H.M. Murphy: None. **C.H. Wideman:** None.

Poster

515. Working Memory: Prefrontal Cortex I

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Topic: H.01. Animal Cognition and Behavior

Support: CONACyT (280424 and PN-2016-01-465)
PROFOCIE UCOL-CS 2014-2017

Title: Maternal high-fat diet during pregnancy effects on working memory performance and glutathione levels in the rat offspring at young age

Authors: *N. Y. CORTÉS[1], C. R. VUELVAS-OLMOS[1], R. PEDRAZA-MEDINA[2], M. F. PINTO-GONZALEZ[1], N. Y. PEÑA-GARCIA[2], J. L. COLLAS-AGUILAR[2], J. GUZMÁN-MUÑIZ[2], L. M. BALTAZAR-RODRIGUEZ[1], N. A. MOY-LOPEZ[2];
[1]Sch. of Med., [2]Sch. of Psychology, Univ. of Colima, Colima, Mexico

Abstract: Introduction: The environment that a developing offspring experiences during the perinatal period is markedly influenced by maternal health and diet composition. The quantity and quality of dietary fats consumed during pregnancy have critical role in programming the neural circuitry that regulates cognitive processes. Cognitive processes, such as working memory, allows organisms to interact with the environment and to acquire knowledge/information. **Aim:** To analyze the effects of a high-fat diet (HFD) during gestation on working memory and glutathione (GSH) levels in the Wistar rat pups at young age. **Study design:** We used 30 pups: 15 pups from a mother fed balanced diet (BD) (6.2% fat energy) and 15 pups from a mother fed an HFD (42% fat energy) during pregnancy. Since postnatal day 3 (PND3) body weight was measured daily. Posteriorly, since PND 28 to 42, using the Eight-Arm Radial Water Maze, was assessed working memory (indicators: correct/incorrect working memory and reference memory errors). After the behavioral evaluation, a blood sample was collected and blood serum was obtained. Subsequently, the ELISA technique was performed to identify the serum GSH levels. The experiments and treatments were conducted in compliance with the Norma Oficial Mexicana-062-ZOO-1999 and the Ethics Committee of School of psychology of the University of Colima approved the study protocol. **Results:** About weight gain were no significant differences between groups ($p>0.05$), but HFD pups showed a tendency to a higher increase in body weight on last weeks. About the working memory assessment, there was significant difference in all parameters evaluated ($p<0.05$). Also, HFD pups showed significantly lower serum GSH levels at PND42 ($p=0.001$). A correlation was found between the GSH serum levels and the correct working memory errors ($r=0.81$, $p<0.05$). **Conclusion**: Exposure to a maternal HFD during pregnancy cause working memory deficits and decrease the GSH levels. An imbalance between the production of pro-oxidants as a result of cellular metabolism and antioxidants, oxidative stress results. Therefore, GSH decrease may indicate an increase in oxidative stress. The mechanisms by which maternal diet and metabolic profile shape the perinatal environment remain largely unknown, but due to correlation between the alterations, we could hypothesize that this is one mechanisms causative that affect the environment of the developing offspring. Given the high rates of obesity and high fat diet consumption in pregnant women, it is vital continue to examine the influence that maternal nutrition and metabolic profile have on the developing offspring.

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Poster

515. Working Memory: Prefrontal Cortex I

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Program #/Poster #: 515.03/AA23

Topic: H.01. Animal Cognition and Behavior

Support: NIH R01EY026924
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Research to Prevent Blindness Inc., New York, NY

Title: Frontal eye field inactivation modulates beta rhythms within V4 cortex

Authors: *M. PARTO DEZFOULI[1], M. ZAREI[2], M. I. VANEGAS[3], M. DALIRI[1], Z. BAHMANI[4], B. NOUDOOST[3];
[1]Dept. of Biomed. Engin., Iran Univ. of Sci. and Technol., Tehran, Iran, Islamic Republic of; [2]Dept. of Electrical Engineering, Sharif Univ. of Technol., Tehran, Iran, Islamic Republic of; [3]Dept. of Ophthalmology and Visual Sciences, Univ. of Utah, Salt Lake City, UT; [4]Sch. of Cognitive Sci., Inst. for Res. In Fundamental Sci., Tehran, Iran, Islamic Republic of

Abstract: Spatial working memory (WM) modulates alpha-beta oscillations of local field potentials (LFPs) within extrastriate visual areas. These areas receive a strong signal from the Frontal Eye Field (FEF) carrying the content of WM. In order to examine the necessity of FEF in driving these WM-induced oscillatory changes, we pharmacologically inactivated FEF and simultaneously recorded the spiking activity and LFPs in the V4 cortex of macaque monkeys using linear array electrodes. The animals performed a modified version of the memory-guided saccade task. In this task, the animal needs to remember the location of a cue throughout the delay period. In order to drive V4 neurons and assess the interaction between spatial WM and sensory processing, we added an oriented grating, with different contrasts and orientations, as a task-irrelevant background. We focused on V4 neurons with visual receptive fields overlapping with the FEF's motor field (defined as the endpoint of saccades evoked by FEF electrical stimulation). After finding overlapping FEF-V4 sites, a portion of FEF was inactivated by local injection of 0.5-1.0 μL of the GABA-a agonist muscimol. The FEF inactivation impaired the behavioral performance: it increased the saccade errors and reaction times of monkeys for the location corresponding to the part of space represented at the injection site. FEF inactivation reduced the strength of visual signals, in terms of orientation and contrast discrimination, within the overlapping V4 area. Moreover, within V4, the Beta power and amplitude of LFPs were reduced by FEF inactivation. The locking of spike times to the phase of LFPs, in the Beta range, was also diminished. Together, these findings show that WM-driven oscillations in V4 depend upon the FEF, and demonstrate how a spatially specific WM signal from prefrontal cortex is capable of changing visual representation within extrastriate cortex.

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Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.04/AA24

Topic: H.01. Animal Cognition and Behavior

Support: BBRF Research Grant (25239)

Title: Thalamic amplification of cortical connectivity supports short-term maintenance of sensory history

Authors: *L. I. SCHMITT, M. M. HALASSA;
MIT, Cambridge, MA

Abstract: The thalamus is the major input to the cortex and interactions between these structures are critical for cognition. While the thalamus is often thought of as a simple relay carrying information to or between cortical regions, a view derived from early studies of sensory thalamic nuclei, recent anatomical and functional data suggest that such an oversimplified model is unlikely to capture the involvement of the thalamus in many cognitive functions. This is particularly true in the case of "higher-order" thalamic nuclei such as the mediodorsal (MD) and Lateral Posterior (LP) which are primarily connected to cortical circuits and receive little input from the sensory periphery. While lesion studies suggest these nuclei are critical for cognition, incomplete understanding of their function makes it difficult to determine whether this is a cause or consequence of dysfunctions seen in complex neurodevelopmental disorders. Previous investigations of into how the MD influences representations of rules used to guide attention in the mouse prefrontal cortex (PFC) showed that the MD sustains rule representations by stabilizing ensemble dynamics among a subset of task-engaged neurons via amplification of effective connectivity. These findings suggest that selective stabilization of cortical networks by thalamic input might be a property of thalamocotical interactions that could enable short-term storage of information, a function that is essential for tasks ranging from understanding language to making inferences about visual scenes. The current study investigates whether this type of interaction supports other types of short-term storage by examining representation of recent sensory inputs in the posterior parietal cortex (PPC). The PPC is a key player in sensory decision-making and recent evidence suggests that one of its roles is to influence responses to current inputs based on sensory history. Using a newly devised feature-based sensory decision-making task we show that behavioral biases from previous trials depended on both the LP and PPC. Both circuits were also necessary for animals to make decisions on trials with ambiguous evidence based on sensory history. Importantly, activation of the LP produced an enhancement

in effective connectivity like that produced by MD activation suggesting that it plays an analogous role in stabilizing cortical representations. Overall, these findings identify a potentially general circuit feature in the mammalian brain, thalamic control of functional cortical connectivity, and suggest that it is essential for cognitive abilities that rely on short term storage of information.

Disclosures: L.I. Schmitt: None. **M.M. Halassa:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.05/AA25

Topic: H.01. Animal Cognition and Behavior

Title: Reversal of an MK-801 induced working memory deficit by the D1 agonist SKF-81297 in a rodent touchscreen test

Authors: R. WYLER[1], M. HAMAN[1], B. KUENNECKE[2], ***E. C. O'CONNOR**[1];
[1]Neurosci. and Rare Dis., [2]Biomarkers and Translational Technologies, F. Hoffmann-La Roche, Basel, Switzerland

Abstract: Working memory impairments feature in many neuropsychiatric and neurological conditions. Disruption of NMDA receptor signaling may represent a common neural substrate for this deficit, while stimulation of dopamine D1 receptors is proposed as a potential pro-cognitive therapy. Here we explored this topic using a rodent touchscreen-based task of spatial working memory, namely trial-unique delayed nonmatching-to-location (TUNL). Male Lister Hooded rats were trained in TUNL until reaching stable performance criteria. Probe sessions were conducted in which the delay between sample and choice stages of individual trials varied from 2 to 6 seconds, leading to a delay-dependent decrement in choice performance. The NMDA receptor antagonist MK-801 (0.025-0.1 mg/kg) induced a dose-dependent impairment of choice performance during probe sessions, while ketamine (2.5-7.5 mg/kg) dose-dependently suppressed trial initiation without impairing choice performance. The D1 agonist SKF-81287 reversed the MK-801 induced working memory deficit in TUNL, but only at doses approximately 10-fold lower than those giving rise to typical D1-dependent locomotor hyperactivity. Pharmacological Magnetic Resonance Imaging (phMRI) revealed that SKF-81297 induced distinct circuit activation patterns at pro-cognitive vs. pro-motor dose levels, providing circuit insight to the observed behavioral effects. We discuss TUNL as a paradigm with translational relevance for assessing mechanisms underlying working memory, and which may facilitate the identification of future therapies for brain disorders where cognition impairment remains of high unmet medical need.

Disclosures: **E.C. O'Connor:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche. **R. Wyler:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche. **M. Haman:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche. **B. Kuennecke:** A. Employment/Salary (full or part-time):; F. Hoffmann-La Roche.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

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Program #/Poster #: 515.06/AA26

Topic: H.01. Animal Cognition and Behavior

Support: NIMH IRP 1ZIAMH002881

Title: Spatial encoding of mPFC neurons during working memory

Authors: *X. MA, H. ZHU, Z. LI;
NIH, Bethesda, MD

Abstract: Working memory is a cognitive system which temporarily maintains and manipulates information to guide behavior. It provides the functional backbone to high-level cognition. Studies in primates have well demonstrated that the dorsolateral prefrontal cortex (dlPFC) is a critical cortical area for working memory. In rodents, lesion or inactivation of the medial prefrontal cortex (mPFC), which has similarities with the primate dlPFC in anatomical connections and function, leads to working memory impairment. Some mPFC neurons fire in response to the events occurring in the working task, such as cues, and choices or have sustained firing during the delay period. In spatial working memory tasks, some neural activities are tuned by spatial information. However, what information is encoded by these activities and how they contribute to working memory remain unknown. To address these questions, we recorded the spiking activity of mPFC neurons during a spatial working memory task and analyzed the correlation between neural activities and space, time and animal behavior. To this end, we implanted tetrodes controlled by a microdrive into the mouse mPFC. After recovery from surgery, the mice were subjected to water restriction and trained for a delayed alternation working memory task in a T-maze. Each trial of the task consists three phases: sample phase, delay phase and test phase. In the sample phase, one of the two arms with a water spout at the end is randomly selected to open and the animal receives water reward if it reaches the spout. In the delay phase, the animal is restrained in a holding area for 10 seconds. In the test phase, both arms containing water spouts are open, and the animal will receive water rewards only if it runs into the arm that it has not been to during the sample phase. Animals made correct choices in 85% of the trials in three consecutive days were recorded for local field potentials and spiking actives during the task. Single unit activities were isolated manually using the Offline Sorter software. A total of 110 single units, including 95 putative glutamatergic neurons and 15 putative

GABAergic neurons, were obtained from 6 mice. 66.4% of recorded single units change firing rates within a 5-second time window before and after reward delivery. Most of these cells were excited before and suppressed after reward delivery, while only a few of them increased activities after reward delivery. Moreover, 29.8% of these cells responded differently to left and right rewards, suggesting that mPFC neurons encode the location of rewards.

Disclosures: **X. Ma:** None. **H. Zhu:** None. **Z. Li:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.07/AA27

Topic: H.01. Animal Cognition and Behavior

Support: NSF EPSCoR Grant 1632738
NIMH Grant MH081162
McKight Foundation Grant

Title: Large-scale non-human primate local field potential dynamics during visual short-term memory

Authors: *S. J. HOFFMAN[1], N. M. DOTSON[2], C. M. GRAY[1];
[1]Cell Biol. and Neurosci., Montana State Univ. Bozeman, Bozeman, MT; [2]Bioengineering, Univ. of California Berkeley, Berkeley, CA

Abstract: Short-term memory is an essential process in cognition. It provides an essential link between sensory input and behavioral output. In object based visual short-term memory a number of operations must unfold rapidly over a widely distributed network of brain areas. Despite much research in this area, little is known about the wide-spread dynamics of the local field potential (LFP) during such cognitive tasks. In order to investigate this process we recorded broadband neural activity in macaque monkeys while they performed an object based delayed match-to-sample task. The recording device enabled the simultaneous recording of neural activity from over 100 intracortical micro-electrodes, across tens of cortical areas, roughly spanning a cortical hemisphere. This allowed the investigation of task dependent LFP spectral power fluctuations, as well as the investigation of task dependent synchronization of multiple narrowband oscillations. Initial findings indicate wide-spread decreases in the beta band power in frontal regions during the memory task. The other frequency ranges investigated (i.e. theta, alpha, and gamma) showed a more heterogeneous and complex activity profile. In parietal areas we found evidence of a decrease in low frequency power coupled with a simultaneous increase in alpha band power. This "sharpening" of the alpha signal is suggestive of a gating-like dynamic

between the low frequencies and the alpha band. These findings will help elucidate the large-scale spatio-temporal dynamics involved in short-term visual memory.

Disclosures: S.J. Hoffman: None. **N.M. Dotson:** None. **C.M. Gray:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.08/AA28

Topic: H.01. Animal Cognition and Behavior

Support: NIH HD87101

Title: Optogenetic inhibition of secondary motor cortex disrupts olfactory working memory in behaving mice

Authors: *A. BELLAFARD, G. NAMVAR, P. GOLSHANI;
UCLA Dept. of Neurol., Los Angeles, CA

Abstract: Working memory is the ability to store information for short periods of time (seconds) in the absence of ongoing sensory input. While a number of brain regions vital for working memory have been identified, and persistent activity in these regions has been recorded during working memory tasks, we still do not understand the mechanisms by which an ensemble of neurons generate these ongoing activity patterns. To gain more insight into this problem, we have trained head-fixed mice to perform an olfactory working-memory task, in which head-fixed mice compare the identity of two discrete odors separated by a five second delay period. To interrogate the functionality of neuronal population in secondary motor cortex, we have utilized highly efficient soma-targeted Guillardia theta anion-conducting channelrhodopsins (GtACRs) expressing virus to conduct time-resolved optogenetic silencing at different time intervals while the animal was performing the task. We have shown that the stimulation during the delay and reward periods greatly worsens task performance, while stimulation at other time intervals has no effect. Our results suggest that the secondary motor cortex is both important for maintaining the working memory during the delay period, as well as comparing the memory of the first stimulus with the second stimulus to drive decision making.

Disclosures: A. Bellafard: None. **G. Namvar:** None. **P. Golshani:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.09/AA29

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant EY026924
NIH Grant EY014800
Research to Prevent Blindness Inc., New York, NY

Title: Impact of spatial working memory on visual processing within V4

Authors: *M. I. VANEGAS[1], W. H. NESSE[1,2], B. NOUDOOST[1];
[1]Ophthalmology and Visual Sci., [2]Mathematics, Univ. of Utah, Salt Lake City, UT

Abstract: Recent studies have shown that extrastriate areas receive the content of working memory (WM) via direct projections from prefrontal cortex (Merrikhi et al. Nat Commun 2017). Extrastriate areas exhibit changes in their oscillations in response to the deployment of WM: the power of alpha-beta oscillations in their local field potentials (LFPs) increases and the spiking activity of neurons in these areas becomes locked to these LFP oscillations (Bahmani et al. Neuron 2018). In spite of receiving the WM signal and exhibiting oscillations in response to it, neurons within extrastriate areas do not reflect the content of WM in their average spiking activity in the absence of visual input. In order to understand how the WM signal affects the extrastriate representation, we examined the influence of WM on these areas in the presence of visual signals. We trained the animal (rhesus macaque) to perform a memory guided saccade task in the presence of a visual stimulus background. In this task, the monkey fixates and a peripheral visual target is presented. The monkey maintains fixation while remembering the target location, and after the fixation point disappears, executes a saccadic eye movement to the remembered location to receive a reward. We recorded the LFP and neuronal activity of extrastriate area V4 using linear array electrodes. The background visual stimulus was an oriented grating covering the full span of the monitor, driving simultaneously recorded V4 neurons irrespective of their receptive field (RF) locations. The orientation (0, 45, 90, 135 degrees) and contrast (0%, 4%, 8%, 16%, 32%, 64%) of the background grating, as well as the locus of WM (toward the V4 RFs or 180 degrees away), were pseudorandomly varied across trials. Preliminary findings show that WM alters the orientation tuning and contrast response function at the level of single neurons, and the representation of visual information at the level of the population. These results indicate that although WM does not alter the average spiking activity of neurons within extrastriate areas in the absence of sensory information, in the presence of sensory input these areas can benefit from the WM signal both at the level of single neurons and the neuronal population.

Disclosures: **M.I. Vanegas:** None. **W.H. Nesse:** None. **B. Noudoost:** None.

Poster

515. Working Memory: Prefrontal Cortex I

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Program #/Poster #: 515.10/AA30

Topic: H.01. Animal Cognition and Behavior

Support: NIH R21NS096936
T32AG049688

Title: Low-dose olanzapine and clozapine effects on spatial working memory performance in rhesus monkeys

Authors: ***N. A. UPRIGHT**, M. G. BAXTER;
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Abstract: Chemogenetic techniques allow for the precise and reversible manipulation of specific cell populations or neuronal circuitry in awake, behaving animals. Designer receptors exclusively activated by designer drugs (DREADDs) are a popular form of this technology utilizing a non-endogenous actuator ligand to activate a modified muscarinic acetylcholine receptor which is no longer sensitive to acetylcholine as an agonist. The first employed DREADD ligand, clozapine-*N*-oxide (CNO), lacks sufficient brain penetrance and is metabolically converted to clozapine making it potentially unsuitable for future translational applications of chemogenetic systems. It is crucial in studies using chemogenetic systems to test the potential effects of DREADD actuators prior to any DREADD transduction, so that effects of DREADDs can be attributed to the chemogenetic system and not the actuator drug itself. We investigated working memory performance after preoperative injections of two DREADD agonists, clozapine and olanzapine, in male rhesus monkeys tested in a spatial delayed response task. Both agonists are FDA-approved antipsychotics, which could facilitate their use in translating DREADD technology to a clinical setting. Also, both drugs have high affinity for muscarinic-based DREADD receptors, so that each may be administered at low doses to activate DREADD receptors while minimizing off-target effects. Monkeys received intramuscular injections at two doses for clozapine, 0.1 and 0.2 mg/kg, and two doses for olanzapine, 0.1 and 0.05 mg/kg. We found that mean performance at 0.1 mg/kg clozapine did not differ from mean performance after vehicle in all four subjects. Administration of 0.2 mg/kg clozapine impaired performance in 2 of the 4 monkeys, with decreased correct trials at higher delay periods. We also found deficits in two monkeys after administration of olanzapine; both were impaired compared to vehicle after the 0.1 mg/kg dose and one also showed deficits at 0.05 mg/kg. DREADDs remain a powerful tool to remotely manipulate neuronal activity *in vivo*. These data demonstrate

the importance of including preoperative actuator drug injections in experimental studies with DREADDs, to confirm in each subject that the actuator drugs are without effect on their own. Additionally, it remains important to ensure that all ligands are administered at appropriate doses to minimize potential effects at endogenous receptors. We speculate that the unique neuropharmacology of prefrontal cortex function makes the primate prefrontal cortex especially vulnerable to off-target effects of DREADD actuator drugs with affinity for endogenous monoaminergic receptor systems.

Disclosures: **N.A. Upright:** None. **M.G. Baxter:** None.

Poster

515. Working Memory: Prefrontal Cortex I

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Topic: H.01. Animal Cognition and Behavior

Support: National Research Foundation of Korea funded by the Ministry of Science and ICT 2016M3C7A1913844
National Research Foundation of Korea funded by the Ministry of Science and ICT 2016941946

Title: Anxiety induced working memory disruption was mediated by amygdala-ventral hippocampal circuit

Authors: *J. CHOI, Y. JEONG;
KAIST, Daejeon, Korea, Republic of

Abstract: Cognitive functions can be impacted by anxiety. In particular, anxiety is regarded to restrict a capacity of working memory by competing with task-relevant processes. Previous studies have shown that when people feel anxiety, working memory problem appears. However, it is still elusive that how anxiety-related brain circuits affect working memory dysfunction. In this study, mice were allowed to conduct working memory task when they felt anxiety which was induced by an anxiogenic drug or optogenetic stimulation. Simultaneous electrophysiological recordings were also performed to verify neural underpinnings of working memory dysfunction in anxious period. During the nonmatch-to-place T-maze task, one of the typical behavior tasks for measuring working memory function, mice showed significantly reduced performance when the anxiogenic drug (picrotoxin) was injected intraperitoneally. Optogenetic inhibition of the circuit from basolateral amygdala to the ventral hippocampus, which was previously reported as an anxiogenic circuit, restored the working memory disfunction by the drug. In the same vein, optogenetic excitation of the circuit also significantly reduced the working memory function during the task. Moreover, delay period-specific

excitation also significantly reduced working memory function and the impairments depended on a delay time (the longer delay time, the more impariments), suggesting that anxiety might be a disturbance factor for maintaining the working memory ability. Results of local field potentials and single unit recordings in medial prefrontal cortex (mPFC), basolateral amygdala (BLA), and ventral hippocampus (vHPC) was showed that coherence between mPFC and vHPC was weakened during the maintaining period of working memory in anxious situations. In addition, pattern of the mPFC units was diminished when the mice showed working memory deficit in anxious status. Thus, this study suggests that, when mice feel anxiety, BLA to vHPC circuit mediates working memory disruption, which involved mPFC dysfunction.

Disclosures: **J. Choi:** None. **Y. Jeong:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

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Topic: H.01. Animal Cognition and Behavior

Support: EU-H2020-FET 1564
Foundation Adelis
ERC CoG 819496
Adelis Foundation
Human Frontier Science Program

Title: Putative roles of inhibitory interneuron subtypes in working memory

Authors: *P. PATIL, M. KATKOV, O. YIZHAR, M. V. TSODYKS;
Weizmann Inst. of Sci., Rehovot, Israel

Abstract: Working memory is an essential human cognitive process required for all cognitive activities. Recent studies from our group (Mi et. al. 2017, Mongillo et. al. 2008) have proposed a mechanism of working memory based on short-term synaptic plasticity. A critical component of this model is a central inhibition which prevents multiple item representations from being active at the same time. We know from experimental studies that multiple genetically-defined interneuron subtypes [predominantly parvalbumin (PV), vasoactive intestinal peptide (VIP) and somatostatin (SOM) expressing neurons], each with unique excitability and connectivity properties, mediate inhibition in the cortex. However, the specific role these populations play in working memory is poorly understood. Previous models of working memory lack specific mechanisms for regulating the load of working memory. We addressed this by including interneuron subtypes in the model and exploring the resultant dynamics to probe the functional roles of these subtypes in working memory. We used a simplified model of connectivity and

synaptic parameters based on the literature. Our simulations suggest that incorporation of these three distinct inhibitory motifs in the model allows for the active control of working memory. Specifically, we suggest that the PV expressing interneurons are responsible for one-at-a-time activation of items by implementing “winner-take-all” dynamics of working memory. We propose that SOM expressing interneurons and their facilitating excitatory inputs are responsible for the short lifetime of an item in working memory. We further propose that VIP expressing interneurons prolong the maintenance of items in working memory by inhibiting SOM neurons. We predict that external excitatory input to VIP should increase task performance. We therefore postulate that a diversity of interneuron subtypes, matching the properties of the three major interneuron populations in cortex, is an integral component of the active control of working memory. The presented model makes concrete, experimentally testable predictions for manipulation of inputs to these interneuron subtypes, consistent with the known literature.

Disclosures: P. Patil: None. **M. Katkov:** None. **O. Yizhar:** None. **M.V. Tsodyks:** None.

Poster

515. Working Memory: Prefrontal Cortex I

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Program #/Poster #: 515.13/AA33

Topic: H.01. Animal Cognition and Behavior

Support: NIMH093354

Title: Cholinergic modulation of working memory performance and delay-related firing via actions at muscarinic M1 receptors and KCNQ potassium channels in dlPFC

Authors: *V. C. GALVIN[1], S. YANG[2], Y. YANG[4], L. E. JIN[5], A. S. LOWET[6], H. GAITSCH[3], T. C. LIGHTBOURNE[7], A. F. ARNSTEN[8], M. WANG[9];
[1]Neurosci., [2]Dept. of Neurobio., [3]Yale Univ., New Haven, CT; [4]Penn State Univ., Hershey, PA; [5]Weill Cornell Med., New York, NY; [6]Neurosci., Harvard Univ., Cambridge, MA; [7]Mental Hlth., New York State Med., New York, NY; [8]Neurosci., Yale Univ. Sch. Med., New Haven, CT; [9]Neurosci., Yale Univ. Sch. of Med., New Haven, CT

Abstract: The dorsolateral prefrontal cortex (dlPFC) is critical for working memory, and electrophysiology studies have found neurons in this region that exhibit persistent activity over delay periods in working memory tasks in the absence of continued sensory input. This persistent activity arises from recurrent excitation within microcircuits of pyramidal cells in deep layer III of primate dlPFC. These excitatory glutamatergic connections require NMDA receptor activation, and previous work has shown acetylcholine (ACh) plays a critical role in NMDA receptor activation via actions at nicotinic a7 receptors concentrated within the postsynaptic density (PSD) on dendritic spines. This follow-up study investigated the role of metabotropic

muscarinic M1 receptors (M1Rs), which are also highly expressed in cortex and found postsynaptically within or immediately proximal to the PSD on dendritic spines in layer III of primate dlPFC. These receptors are known to regulate KCNQ potassium channels, or "M" channels, which are also expressed at the synapse in dlPFC. As such, closure of these "M" channels following M1R activation may contribute to the permissive role of ACh in these circuits. Our data show M1R and KCNQ channels also play a critical role in persistent activity in primate dlPFC, as activation of M1R enhances delay-related firing, and this can be reversed by opening KCNQ channels. Additionally, blockade of M1R erodes delay-related activity, and this reduction is reversed by closure of KCNQ channels. As ACh release and cholinergic receptor expression can be reduced or altered in patients with various psychiatric disorders, we also tested the effects of systemic delivery of an M1R positive allosteric modulator (PAM) to determine if targeting M1R my be a useful therapeutic strategy. Our study finds that low doses of M1R PAM consistently improves working memory performance in primates, and support continued pursuit of this receptor as a potential treatment for PFC dysfunction.

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Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.14/AA34

Topic: H.01. Animal Cognition and Behavior

Support: NIH: R01 EY027036
Simons Collaboration on the Global Brain 542989SPI

Title: Model of temporal integration through recurrent feedback and synaptic facilitation

Authors: *R. A. BAARDA[1], D. L. COX[1], E. R. F. AKSAY[3], M. S. GOLDMAN[2];
[1]Dept. of Physics, [2]Ctr. for Neurosci. and Depts. of Neurobiology, Physio., & Behavior, and Ophthalmology & Visual Sci., UC Davis, Davis, CA; [3]Inst. for Computat. Biomedicine and Dept. of Physio. and Biophysics, Weill Med. Col. of Cornell Univ., New York, NY

Abstract: The oculomotor integrator network is a convenient model system for investigating the circuit mechanisms of working memory. This network receives eye velocity commands as inputs and integrates these to yield eye position commands. The eye position is represented by the collective activity of two opposing neural populations, which exhibit a threshold-linear increase in their firing rates as the eye is held at more ipsilateral positions and decrease their firing when the eye is more contralateral. These firing rates are maintained until the animal makes a saccade

to a new position, yielding a persistence time of ~10 seconds in the dark that far exceeds any known synaptic or intrinsic time constants in the system. This study focuses on how short-term synaptic plasticity may help to both coordinate the neural populations and extend the duration of persistent firing. Previous work (Fisher et al., Neuron 2013), which modeled the effects of inactivating part of the integrator network, suggested the presence of a slow cellular or synaptic process that increases superlinearly with firing rate. Motivated by the observation that synaptic facilitation has prominent slow kinetics in other working memory systems (Wang et al., Nature Neuroscience 2006) and leads to a superlinear response as firing rates are increased, we constructed a model in which synaptic connections exhibit predominantly facilitating dynamics. This model has a bilateral architecture in which each population excites itself and inhibits the opposing population. Due to the superlinearity of the synaptic facilitation, each population primarily controls the eye position in the portion of the ocular range corresponding to its own high firing rates. This feature leads to approximately independent control of each half of the animal's eye movement range, consistent with pharmacological inactivation studies of the effects of silencing one side of the integrator circuit. In addition, a de-tuned version of the model produced slower drift rates compared to the equivalent model with no synaptic facilitation, suggesting that synaptic facilitation may provide an intrinsic synaptic contribution to the long integration time scales seen in this system.

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Poster

515. Working Memory: Prefrontal Cortex I

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Program #/Poster #: 515.15/AA35

Topic: H.01. Animal Cognition and Behavior

Support: MRC intramural program MC-A060-5PQ14

Title: Local field potentials contain stronger and more stable information than spikes

Authors: *S. SHASHIDHARA[1], K. WATANABE[2], M. KUSUNOKI[3], M. KADOHISA[4], M. J. BUCKLEY[5], J. DUNCAN[6];
[1]MRC Cognition and Brain Sci. Unit, Cambridge, United Kingdom; [2]Ctr. for Information and Neural Networks, Natl. Inst. Information & Communications Technol., Suita City, Japan; [4]Exptl. Psychology, [3]Univ. of Oxford, Oxford, United Kingdom; [5]Oxford Univ., Oxford, United Kingdom; [6]Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Though working memory has long been associated with sustained firing in prefrontal and parietal cortex, attention has recently been focused on dynamic coding, with neurons

showing stable encoding of spatial information for only brief periods. Here we studied stable vs dynamic encoding in both spike rate and local field potential (LFP) signals. We obtained data from two adult male rhesus monkeys (Macaca mulatta) performing a spatial working memory task. On each trial, the animal was shown an array of five locations, awaited a go signal, then reached out to touch one location. A feedback signal and reward indicated whether or not this location was correct. In a first set of trials (cycle 1), the animal explored different locations until the target was discovered. In a subsequent three cycles (exploit phase), the monkey chose the location previously learned to be correct. Animals were extensively trained, with close to perfect performance. In each animal, neuronal activity was recorded from two chambers located over lateral frontal and inferior parietal cortex.
Both the firing rate of single neurons and the voltage recorded on single LFP channels differed across locations, thus encoding spatial information. To examine stability, we performed a cross-temporal generalization analysis, asking how patterns of activity at one trial time correlated with patterns at other times. For spike rate, activity patterns changed rapidly over time and phase of the trial (pretrial, choice array, go signal and movement, feedback). For LFPs, in contrast, a strong signal of target location remained largely constant across time. This target information arose post positive feedback in the explore phase and remained stable throughout the exploit phase. LFPs are influenced by multiple sources of voltage fluctuation in the extra-cellular matrix, integrated over a local region of tissue. Though the firing of individual neurons may be closely locked to specific time-points and/or trial events, the LFP signal is more stable, reflecting integration of multiple signals over a local cell population.

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Poster

515. Working Memory: Prefrontal Cortex I

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Program #/Poster #: 515.16/AA36

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant EY025768

Title: A task-irrelevant visual perturbation reveals hidden information from a spatial working memory network

Authors: *D. Y. JUNG[1], J. ROZOWSKY[2], A. C. SNYDER[3,1,4];
[1]Neurosci., [2]Computat. Biol. and Chem., [3]Brain and Cognitive Sci., [4]Ctr. for Visual Sci., Univ. of Rochester, Rochester, NY

Abstract: Working memory (WM) relies on a network distributed across multiple cortical regions, especially involving the prefrontal and posterior parietal cortices. This network is differentially activated while a memory item is maintained**.** This maintenance activity was conventionally described as elevated and sustained neuronal spiking activity reflecting the quantity of items in WM. Recent studies question this view, however, because this activity can be hidden and often selective to external cues (e.g., reward). Such hidden states are particularly difficult to assay at the network level, where tools such as single neuron recording are prohibitive. Electroencephalography (EEG) can measure large-scale network activity, but measuring hidden neural states with EEG is even more challenging. Previous work has demonstrated that a task-irrelevant, but strongly effective, visual stimulus during the maintenance period of a WM task perturbs the hidden state of WM, evoking a response that can improve decoding of remembered information. We employed this method to noninvasively perturb the hidden neural state of WM of a rhesus monkey performing an oculomotor delayed response (ODR) task while we recorded 32 channels of EEG at its scalp. We hypothesized that this strong noninvasive perturbation would improve our ability to decode spatial features of the memory item from EEG signals during the maintenance period of the ODR task. We indeed found that the irrelevant stimulus improved decoding of remembered spatial information. This shows that spatial features of memory items are maintained in the hidden neural state of WM beyond the information provided by maintenance period spiking activity. Combining this network-level analysis of WM mechanisms via non-human primate EEG with multi-area population-level analysis of neuronal spiking activity will improve our understanding of the function of the brain networks underlying working memory performance.

Disclosures: D.Y. Jung: None. **J. Rozowsky:** None. **A.C. Snyder:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.17/AA37

Topic: H.01. Animal Cognition and Behavior

Support: DFG - SFB 1315
DFG - NeuroCure EXC 257

Title: Automated touchscreen test battery for group-housed mice: TUNL, 5CSRTT and the use of moving visual stimuli

Authors: D. ATTALLA, K. STUMPENHORST, ***Y. WINTER**;
Humboldt Univ. - Inst. fuer Biologie, Berlin, Germany

Abstract: Existing rodents behavioural testing protocols that measure aspects of cognitive decline incorporate food deprivation and animal handling, which can induce stress, anxiety and impulsive behaviour. This in turn may affect the variability and reproducibility of the data. The present study developed a free-feeding, self-motivated, automated touch screen test battery for group housed mice, in which most of the food is collected during task performance throughout the day. C57BL/6J ID-chipped mice, about 15 weeks old, were tested in a 24/7 automated system consisting of a touch screen equipped operant chamber connected to the home cage through a RFID-based sorting system (Fig.1a, ID-Sorter, PhenoSys). Different cognitive domains were examined in the automated system: working memory was assessed using a spatial location task (TUNL), and sustained attention and response inhibition were assessed using the five-choice-serial-reaction-time-task (5CSRTT). Moreover, both visual discrimination and reversal learning were tested. For visual discrimination, we compared performance on signals differing in one feature (2 static images) versus two features (two images, moving in different directions). Mice successfully learned the different behavioural tasks and were sensitive to increasing difficulties (Fig.1b-1d). Importantly, self-motivated mice acquired the tasks in time frames comparable to previous protocols. Mice needed on average 8 days to learn the TUNL, 16 days for the 5CSRTT, and a week for the visual discrimination learning. Furthermore, in our automated experimental setup mice acquired the tasks with performance levels comparable to previous protocols, while avoiding handling and food deprivation.

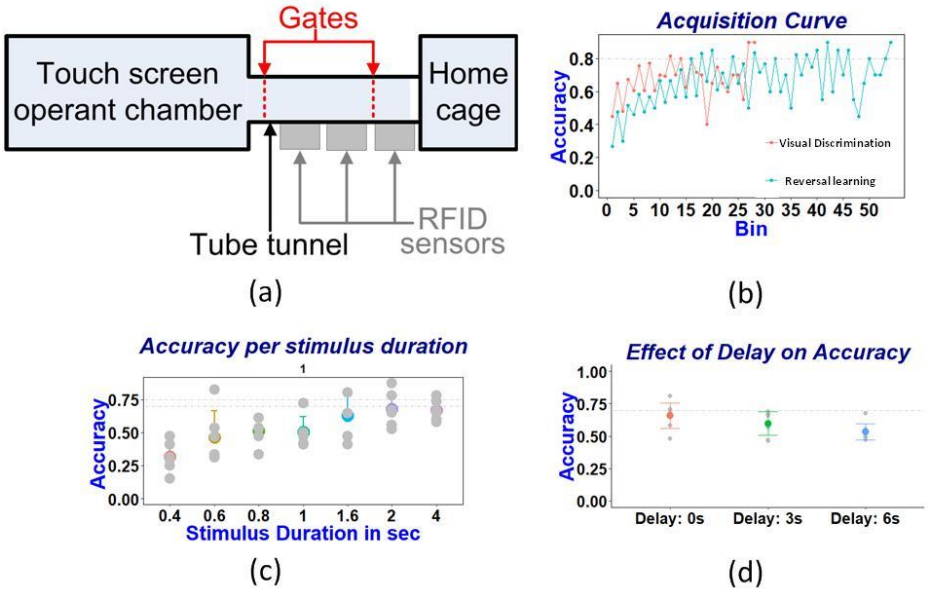

Figure 1: a) Automated touchscreen experimental setup, b) Visual discrimination and reversal learning acquisition, c) 5CSRTT: Data show better performance during long stimuli durations compared to shorter ones, d) TUNL task: Effect of delay (mixed spatial separation).

Data presented as mean ± SD. Data from n=6-7 mice.

Disclosures: **D. Attalla:** None. **K. Stumpenhorst:** None. **Y. Winter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); owns PhenoSys equity.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

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Program #/Poster #: 515.18/AA38

Topic: H.01. Animal Cognition and Behavior

Title: Examinations into the effects of serotonin 5-$HT_{1A/1B}$ agonist on working memory

Authors: *A. E. PAHUA, B. OLIVER, M. EMERY, A. GUTIERREZ, Y. VALENZUELA, D. AMODEO;
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Abstract: Obsessive-compulsive disorder (OCD) is the fourth most prominent neuropsychiatric condition with an estimated lifetime prevalence of 2.5% of the US population. The core symptoms of OCD include obsessive thoughts, repetitive and compulsive behaviors, uncontrollable urges and impulses, ultimately restricting daily functioning. Previous animal studies have found that serotonin 1A and 1B receptor (5-$HT_{1A/1B}$) activation in the brain exacerbates repetitive behaviors, and enhance behavior flexibility and spatial working memory as well. The current studies examined the effects of repeated systemic 5-HT1A/1B receptor activation on the expression of repetitive behaviors in C57BL/6J mice. Mice received repeated injections of 0, 0.1 or 1.0 mg/kg RU24969 during a delayed alternation task (DAT). For DAT, mice were tested in a three arm radial maze. To obtain food rewards, mice learned to enter the last arm they visited such that peak performance would lead alternations amongst all three arms. Mice received 16 trials with a 60 sec delay inter trial interval. Mice were tested daily until reaching a learning criterion of 80% correct choices for two consecutive days. Results demonstrate that higher dose of 1.0 mg/kg RU24969, significantly impaired performance on the DAT task. As predicted, the higher dose of RU24969 significantly increased the days needed to reach learning criterion. This increase was not due to an overall sedative affect as evidenced by comparable rates of locomotor activity. These findings demonstrate that increased 5-HT1A/1B receptor activation led to impaired working memory performance in C57BL/6J mice. In sum, this highlights how specific serotonin modulation be the underlying alteration that impairs working memory in OCD individuals.

Disclosures: **A.E. Pahua:** None. **B. Oliver:** None. **M. Emery:** None. **A. Gutierrez:** None. **Y. Valenzuela:** None. **D. Amodeo:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.19/AA39

Topic: H.01. Animal Cognition and Behavior

Title: Consolidation of long-term object memory in C57BL/6J mice is enhanced by systemic administration of a dopamine D1 agonist, or post-training exposure to a novel context

Authors: *B. L. HINDMAN[1], J. V. BARAN[2], R. W. STACKMAN, JR[1];
[1]Dept. of Psychology, [2]Max Planck Honors Program, Florida Atlantic Univ., Jupiter, FL

Abstract: Memories of a particular event or experience are often more vividly remembered if the event included a novel or surprising feature. Previous research has indicated that this memory-enhancing effect is thought to depend on novelty-induced dopamine neurotransmission in the hippocampus. Further, dopamine or stimulation of D1-like receptors are thought to enhance the consolidation of short-term memory into long-term memory via plasticity related events known as long-term potentiation. To further investigate dopamine related memory enhancements in C57BL/6J male mice, we first examined the influence of the dopamine D1 receptor agonist, SKF81297, on the consolidation of object memory. A modified version of the novel object recognition task was used to test the D1 agonist's differential effects on strong and weak forms of object memory, defined by the amount of time the mice were permitted to explore two novel objects during the sample session; the more time the mice explored, the stronger the memory, as inferred from the preference mice exhibited for a novel object during the test session presented 24 h later. Regardless of the strength of the object memory, systemic administration of SKF81297 prior to the sample session significantly enhanced object memory. These results suggest that D1 receptor activation enhanced the encoding and or consolidation of object memory in mice. Next, we examined the effects of post-sample session exposure to a novel context on the consolidation of object memory. Mice completed a weak or strong sample session and 30 min later, explored a novel context (clear Plexiglas arena containing 160 decorative fillers, and 1% acetic acid) or the empty Plexiglas arena (control condition) for 5 min. The test session was presented 23.5 hr later. Mice that explored the novel context following the sample session exhibited significantly enhanced object memory 23.5 hrs later, regardless of whether the mice received a weak or strong training protocol. Future studies will examine the effects of local D1 receptor activation in the dorsal hippocampus as the site of memory-enhancing effect of SKF81297, and seek to identify whether the novelty-induced memory enhancement is dependent upon dopamine innervation of the hippocampus from the locus coeruleus or the ventral tegmental area.

Disclosures: B.L. Hindman: None. **J.V. Baran:** None. **R.W. Stackman:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.20/AA40

Topic: H.01. Animal Cognition and Behavior

Support: NSFC Grant 81671268

Title: Left hippocampal CA3 not right CA3 dominate spatial working memory

Authors: *H. QING[1], **D. SONG**[1], Q. YANG[1], D. WANG[2], Z. XIE[1], Y. YAN[1], Z. QUAN[1]; [1]Beijing Inst. of Technol., Beijing, China; [2]Shanghai University of Traditional Chinese Med., Shanghai, China

Abstract: Hippocampal CA3 is known to contribute to spatial working memory, but which stage of spatial working memory the CA3 neurons act on is still obscure. And whether lateralization of CA3 function affect spatial working memory is elusive. Here, through using fiber photometry, we found that increased activity of hippocampal CA3 in both sample and choice phases of T maze working memory task, while left CA3 region, not right CA3, showed different activities in choice phases between correct and error trials. Single unite recoding also suggested that proportion of responsive-to-choice-phase neurons in left CA3 was higher than that in right CA3 and left CA3 neurons tended to fire earlier than right CA3 neurons. Optogenetic inhibition of left CA3 neurons during choice phases disrupted spatial working memory, but inhibition of right CA3 neurons had no such effect. The behavioral performance can transfer from T-maze to delay-match-to-place water maze and delayed nonmatching-to-location (TUNL) task in touchscreen-equipped operant conditioning chambers. The findings suggested that the asymmetry of hippocampal CA3 in spatial working memory and left CA3 plays a dominant role in retrieval phase of spatial working memory.

Disclosures: H. Qing: None. **D. Song:** None. **Q. Yang:** None. **D. Wang:** None. **Z. Xie:** None. **Y. Yan:** None. **Z. Quan:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.21/AA41

Topic: H.01. Animal Cognition and Behavior

Support: 225270172001

Title: The magic number of 7: A novel paradigm for assessing capacity of olfactory working memory in mice

Authors: *G. HUANG;
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Abstract: Short term memory is famously limited in capacity to Miller's (1956) magic number 7 ± 2.
Declined working memory capacity are suggested to be the earliest symptoms observed in mild cognitive impairment, Alzheimer's disease and schizophrenia. Although the capacity of working memory is widely studied in healthy subjects and neuropsychiatric patients, there remains lack of tasks to examine capacity of working memory in rodents. The present studies describe a novel olfactory task of working memory capacity, which assesses the ability to remember the numbers of odors in mice. The task was divided into 4 phase, context adaptation phase, no-match rule learning phase, platform training phase, capacity test phase. We found the correction rate was gradually increased from 50% to 90% during the no-match rule learning phase and platform training phase, indicating that mice learn to recall the which odor is the new odor to get food pellets. During the capacity test phase, we found the number that the mice could remember was 7±2, which is similar to the Miller's magic number in humans. Then using the 5×FAD transgenic mice, a widely used animal model of Alzheimer's disease, we found the capacity of transgenic mice is significantly reduced compared that of wildtype mice. Lastly, we found that Fos is significantly decrease in PFC of 5×FAD mice after capacity test, and the number of Fos protein was correlated with the span length during the test. In conclusion, we developed a novel paradigm to assess the capacity of olfactory working memory in mice. We found a "magic 7" rule of span length in mice which indicates mice may shared similar neural basis of capacity of working memory with humans.

Disclosures: G. Huang: None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.22/AA42

Topic: H.01. Animal Cognition and Behavior

Support: UTS Faculty of Science
UTS Center of Health Technologies

Title: The effects of maternal electronic cigarette exposure on offspring behavior and epigenetics

Authors: *T. NGUYEN[1], G. E. LI[1], H. CHEN[1], C. G. CRANFIELD[2], K. C. MCGRATH[1], C. A. GORRIE[1];
[1]Fac. of Science, Sch. of Life Sci., [2]Univ. of Technol. Sydney, Sydney, Australia

Abstract: Electronic cigarettes (e-cigs) are battery-powered devices that convert an oily flavored liquid into an aerosol, and they may or may not contain nicotine. E-cigs are increasingly being used as tobacco cigarette substitutes and there is a growing perception in pregnant women that using e-cigs is safe. However there is little evidence to support this perception. Here we have trialled a maternal model of e-cig exposure and compared the neurological effects on the offspring at different ages. Firstly, Balb/C female mice (n=8/group) were exposed to either ambient air (Sham), e-cigs with nicotine (Ecig+nic) or e-cigs without nicotine (Ecig-nic) to determine whether e-cigs alone had an effect. Then, mimicking a common scenario, mice were switched from tobacco exposure to e-cig exposure during pregnancy: Balb/C female mice (n=8/group) were exposed to either ambient air (Sham), tobacco cigarette smoke (TCS) or exposed to TCS before gestation followed by e-cigs with nicotine (Switch). The period of exposure was 6 weeks prior to gestation, during gestation and lactation. Offspring at 12 weeks old underwent behavioral assessments; Novel Object Recognition (NOR) to study short-term memory and the Elevated Plus Maze (EPM) to study activity and anxiety. Brain tissue (collected at postnatal day (P)1, P20 and Week 13) was processed to analyse global DNA methylation, epigenetic gene changes, and the number of neurons in the dorsal hippocampus and the lateral amygdala nucleus. The behavioral data revealed that offspring from the Ecig+nic and Ecig-nic group showed changes in short-term memory, activity and anxiety. Compared to the sham group, there was an increase in global DNA methylation in the Ecig+nic and Ecig-nic group, an increase in the TCS group and a mild increase in the Switch group. Epigenetic genes such as AurkA, AurkB, AurkC, Kdm5c, Kdm6b, Dnmt3a, Dnmt3b and Atf2 were altered in the Ecig+nic and Ecig-nic group and changes were highest in the TCS group. No significant changes were observed in neuronal cell counts in the Ecig+nic and Ecig-nic group. However, there was a significant reduction in neuronal cell counts in the TCS group and this was somewhat alleviated in the Switch group. Our findings in this mouse model show that 1) E-cig exposure during pregnancy results in neurological changes in the offspring. 2) Tobacco smoking during pregnancy resulted in more marked neurological effects and some of these were alleviated by switching to e-cigs during pregnancy, but not all, and not to normal levels. We conclude that e-cigs are not safe to use during pregnancy.

Disclosures: T. Nguyen: None. **G.E. Li:** None. **H. Chen:** None. **C.G. Cranfield:** None. **K.C. McGrath:** None. **C.A. Gorrie:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.23/AA43

Topic: H.01. Animal Cognition and Behavior

Support: NIH Grant AG057914
NIH Grant AG054180
NIH Grant P30 AG038070

Title: Collaborative cross and diversity outbred populations as a tool to understand the effect of aging and genetics on cognitive decline

Authors: *A. R. OUELLETTE, G. CHRUCHILL, C. C. KACZOROWSKI;
The Jackson Lab., Bar Harbor, ME

Abstract: Cognitive performance varies greatly within an aging population, as the genetic makeup of individuals affects susceptibility to cognitive declines [1]. Uncovering the complex genetic mechanism underlying age and genetic interactions require equally complex tools. One such tool is the Collaborative Cross (CC) mouse Genetic Reference Panel (GRP), consisting of genetically unique inbred stains derived from 8 founder strains, 3 of which are wild derived, resulting in 42.2 million genetic variants segregating across the panel [2]. This diverse GRP provides a tool to infer the presence of genetic modifiers of cognitive decline, which can justify and inform the study design of large-scale mapping studies using Diversity Outbred (DO) mice. Here, we performed Contextual Fear Conditioning (CFC) on a set of ten CC strains at 6, 12 and 18 months of age to assess variation in long-term memory as a function of genetic background strain and age. We hypothesized that both genetic background strain and age would have a significant effect on contextual fear memory (CFM). Consistent with our hypothesis, we found a significant effect of Strain ($p=5.49x10^{-7}$) and Age ($p=1.02x10^{-14}$) on CFM performance across the CC strains. This phenotype was highly heritable ($h^2<0.8$), providing strong evidence for the presence of genetic modifiers that would likely be revealed through genetic mapping studies. To identify those possible genetic modifiers, we performed CFM tests in a large group of DO mice, which are genetically unique and ideal for fine mapping of QTLs. Using a 24 month old cohort of DO mice, we did not detect significant QTLs associated with long-term memory performance. However, ongoing studies are underway to assess cognitive performance of DOs at 6, 12 and 18 months of age in order to better match the CC study design. Lastly, we will perform RNAseq analyses on memory relevant brain regions from each of the CC strains tested in order to identify gene co-expression networks that correlate with cognitive outcomes. These may reveal novel targets to delay or prevent cognitive decline in the aging mice. [1] Buckner RL, et al. (2004) [2] Srivastava A, et al. (2017)

Disclosures: **A.R. Ouellette:** None. **G. Chruchill:** None. **C.C. Kaczorowski:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.24/AA44

Topic: H.01. Animal Cognition and Behavior

Support: National Institutes of Health (1R01HL130984)

Title: Chronic sleep fragmentation accelerates age-dependent cognitive decline in human apolipoprotein E4 transgenic mice

Authors: *D. V. NAIR[1], R. VIJAY[2], D. GOZAL[3];
[1]Atlantic Hlth. Systems, Morristown, NJ and Biomed. Res. Inst. of New, Cedar Knolls, NJ; [2]Pediatrics, Univ. of Chicago, CHICAGO, IL; [3]Dept. of Child Hlth., The Univ. of Missouri Sch. of Med., Columbia, MO

Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder in which there is a progressive decline in cognitive function. A great deal of evidence supports the idea that Apolipoprotein E4 (ApoE4) is an important genetic risk factor for Alzheimer's disease (AD). Previous studies from our lab on ApoE-deficient (ApoE-/-) mice showed increased cognitive impairments following chronic intermittent hypoxia during sleep (IH), a characteristic of sleep apnea, a condition that occurs frequently among AD patients. However, the effect of chronic sleep fragmentation (SF), another hallmark of sleep apnea on cognition is not known. Spatial reference and working memory under chronic SF conditions were assessed in transgenic mice expressing human ApoE4 (hApoE4) at 3 age points (3, 11, and 18 months) and their age-matched controls (C57BL/6NTac). After acquisition of the Morris water maze-based spatial task, all mice were exposed to 15 days of chronic SF (7am to 7pm for 3 weeks) or control sleep, and then re-assessed using Morris water maze, forced swim, sucrose preference test and novel object recognition tests. Both chronic SF and advancing age independently increased behavioral deficits in hApoE4 mice. Further studies are being carried out to evaluate the role of oxidative stress. Understanding the neural basis of ApoE4 on learning and memory paradigms, and its deleterious effects during SF can lead to the development of new therapeutic strategies in the treatment of AD patients afflicted with sleep apnea.

Disclosures: D.V. Nair: None. **R. Vijay:** None. **D. Gozal:** None.

Poster

515. Working Memory: Prefrontal Cortex I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 515.25/BB1

Topic: H.01. Animal Cognition and Behavior

Support: Alzheimer's Association Grant #: SAGA-17-418745

Title: Sex differences shape memory capacity declining during aging: Rescue effects of voluntary exercise

Authors: *V. LOFFREDO[1,2], G. TORROMINO[2], F. ESPOSITO[3], M. DE RISI[4], E. DE LEONIBUS[2,4];
[1]PhD Program in Behavioral Neurosci., Sapienza Univ. of Rome, Rome, Italy; [2]Inst. of Cell. Biol. and Neurobio. - IBCN-CNR, Monterotondo Scalo, Italy; [3]IGB - Inst. of Genet. and Biophysics, Naples, Italy; [4]TIGEM - Telethon Inst. of Genet. and Med., Pozzuoli (NA), Italy

Abstract: Alzheimer's disease (AD) has higher incidence in women compared to men, but the biological bases of this increased vulnerability are still unknown. The aim of this study is to identify early markers of aging in female subjects to discover early disease's mechanisms that make them more prone to develop dementia.
Memory Capacity (MC) is the amount of information that can be hold in memory for a specific time interval. MC declines with aging and its decline is a form of mild cognitive impairment with high predictive value for conversion to dementia.
Using the Different/Identical Object Recognition Task (DOT/IOT) that we have developed to study MC in rodents, we found that in conditions of high load female mice do not consolidate information into long-term memory.
Here we report that this early highly specific deficit in memory consolidation predisposes female mice to an accelerated aging in memory performance; furthermore, we show that this MC deficit is related to estrogen-dependent impairment in GluA1 trafficking in the hippocampus, which we have previously shown to be important for MC in male mice (Sannino et al 2012, Olivito et al 2014). One-month voluntary exercise training, which is known to stimulate hippocampal function (Colcombe et al 2003), strikingly rescued the performance of aging female mice.
In conclusion, we identified a cognitive marker of early aging in females, whose mechanisms may be at the base of their major vulnerability to AD. Furthermore, we show that this deficit is sensitive to exercise training, which makes it a valid model to study the molecular pathway underlying its therapeutic efficacy.

Disclosures: V. Loffredo: None. **G. Torromino:** None. **F. Esposito:** None. **M. De Risi:** None. **E. De Leonibus:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.01/BB2

Topic: H.02. Human Cognition and Behavior

Support: NIH R01 MH069456

Title: Online pattern extraction during spatial navigation

Authors: *K. N. GRAVES[1], J. W. ANTONY[2], N. B. TURK-BROWNE[1];
[1]Psychology, Yale Univ., New Haven, CT; [2]Psychology, Princeton Univ., Princeton, NJ

Abstract: When navigating a novel environment, memories are formed about the specific locations visited. This ubiquitous capacity has been demonstrated across species, from rodents to humans. Although such episodic encoding is important for revisiting old locations, it is not sufficient for optimally searching new locations. Rather, it may be more efficient to aggregate across previously experienced locations and make predictions based on their underlying spatial distribution. Previous rodent work has shown that this distributional learning occurs over many days, consistent with the complementary learning systems theory that episodic memories in the hippocampus are gradually consolidated and integrated in the cortex. However, recent computational modeling suggests that the human hippocampus not only encodes episodes but also extracts regularities across these episodes. Thus, the representation of an underlying spatial distribution may become immediately accessible over the course of learning in the hippocampus, prior to offline consolidation. In the current study, participants navigated a virtual water maze, in which, unbeknownst to them, the platform location on each trial was drawn from a Gaussian distribution. While participants demonstrated an increase across trials in navigation through previously learned platform locations, the most significant increase was toward the mean of these locations, which, crucially, was never a platform location itself. To ensure that this apparent distribution-based navigation was not merely incidental to searching for previously learned platforms, we simulated task performance as one of two Gaussian random walks: one with memory for only individual platform locations and one with a representation of the distribution mean. Navigation behavior data matched the outputs of both models equally well in the first half of the task, but the distribution-mean model fit better in the second half of the task. This suggests that participants extracted and updated an internal distribution online and used this knowledge to guide future navigation. We are now running a simplified version of the task in epileptic patients with implanted electrodes, testing whether these online summaries reflect initial work within the hippocampus to support later offline consolidation into cortex.

Disclosures: K.N. Graves: None. **N.B. Turk-Browne:** None. **J.W. Antony:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.02/BB3

Topic: H.02. Human Cognition and Behavior

Support: NSF BCS-1630296
NIH R01NS076856
NIH F32MH116577

Title: A modality-independent network underlies the retrieval of large-scale spatial environments in the human brain

Authors: *D. J. HUFFMAN[1], A. D. EKSTROM[2];
[1]Ctr. for Neurosci., Univ. of California, Davis, Davis, CA; [2]Psychology, Univ. of Arizona, Tucson, AZ

Abstract: Previous research has suggested that body-based cues (e.g., translations, body and head rotations) play a critical role in establishing spatial representations in the rodent brain. These results have led some researchers to question the validity of human neuroimaging experiments, which are typically conducted in the absence of body-based cues, other than those provided by visual information (e.g., Taube et al., 2013 JOCN). We refer to the hypothesis that body-based cues fundamentally influence neural spatial representations as "the modality-dependent spatial coding hypothesis." Alternatively, "the modality-independent spatial coding hypothesis" predicts that spatial representations will be similar between spatial modalities (e.g., Bryant, 1997 Mind Lang). Due to technological limitations, little is known about the influence of body-based cues on neural representations of space in humans. We used novel immersive virtual reality technology (e.g., an omnidirectional treadmill, head-mounted display) to test these competing hypotheses by having participants navigate three cities under differing levels of body-based cues. Our behavioral and fMRI results support the modality-independent spatial coding hypothesis. First, a Bayes factor analysis revealed evidence in favor of the null hypothesis of no difference in the rate of spatial learning between body-based cues conditions. Second, a classification analysis based on putative neural interactions revealed significant classification accuracy between spatial memory retrieval, an active baseline task, and the resting state; however, network interactions were similar for spatial memory retrieval across body-based cues conditions. Third, we observed task-based activations for spatial memory retrieval compared to the active baseline task in brain regions known to play a role in spatial memory (e.g., hippocampus, parahippocampal cortex, retrosplenial cortex); however, a novel whole-brain Bayes factor analysis revealed widespread evidence in favor of the null hypothesis of no difference in task-based activations as a function of body-based cues throughout the brain.

Finally, analyses of single trial patterns of activity (e.g., classification analysis, representational similarity analysis [RSA]) revealed differences between task conditions but not between body-based cues conditions. Together, these findings suggest that vision, rather than differences in body-based cues, plays a primary determinant in how we encode and retrieve spatial information about large-scale environments.

Disclosures: D.J. Huffman: None. **A.D. Ekstrom:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.03/BB4

Topic: H.02. Human Cognition and Behavior

Support: National Institute for Health Research
UCL Biomedical Research Centre
Wellcome Trust
UK Medical Research Council
European Research Council

Title: Theta power and phase-amplitude coupling in the human hippocampus during spatial memory retrieval

Authors: *U. VIVEKANANDA[1], D. BUSH[2], J. A. BISBY[2], B. DIEHL[3], A. MISEROCCHI[3], A. MCEVOY[3], R. RODIONOV[3], M. C. WALKER[4], N. BURGESS[5];
[1]Inst. of Neurol., London, United Kingdom; [2]UCL Inst. of Cognitive Neurosci., London, United Kingdom; [3]Natl. Hosp. for Neurol. and Neurosurg., London, United Kingdom; [4]Inst. Neurol, London, United Kingdom; [5]UCL, London, United Kingdom

Abstract: Theta oscillations have been well documented in the rodent and human hippocampal network during translational movement and mnemonic function. In addition, the modulation of high-frequency activity - namely, the amplitude of gamma oscillations - by the phase of low-frequency oscillations such as theta, termed phase amplitude coupling (PAC), may provide a mechanism for encoding information and coordinating activity within and between brain regions. Here, we used intracranial EEG recordings to examine the role of theta power and phase-amplitude coupling in the medial temporal lobe during spatial memory retrieval. Twelve patients with refractory epilepsy undergoing intracranial EEG monitoring for clinical purposes were asked to perform a self-paced spatial memory task in a desktop virtual reality environment. Patients first navigated toward and memorized the location of four objects that sequentially appeared in the environment (‘encoding’). Patients were then cued with an image of one object (‘cue’), placed back in the environment and asked to navigate toward the remembered location of

that object and make a button-press response. The distance error (patient response location versus true location of object) was used as a metric of mnemonic performance.
We find that task performance correlates well with clinical measures of memory function across patients. In addition, we report an increase in low (2-5Hz) and high (6-9Hz) theta power in both hippocampus and lateral temporal lobe during cue periods compared to baseline, while task performance was associated with increased high theta power only. Finally, we find that task performance is also associated with increased theta-gamma PAC within the temporal lobe. These results imply distinct roles for low and high frequency theta oscillations in human spatial memory function, and point to a role for temporal lobe theta-gamma PAC in accurate memory retrieval.

Disclosures: U. Vivekananda: None. **D. Bush:** None. **J.A. Bisby:** None. **B. Diehl:** None. **A. Miserocchi:** None. **A. McEvoy:** None. **R. Rodionov:** None. **M.C. Walker:** None. **N. Burgess:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.04/BB5

Topic: H.02. Human Cognition and Behavior

Support: ANR – Essilor SilverSight Chair ANR-14-CHIN-0001

Title: Distinct cerebral structures are involved in landmark- vs. geometry-based spatial navigation

Authors: *S. RAMANOËL[1], M. DURTESTE[1], A. BIZEUL[1], A. OZIER-LAFONTAINE[1], M. BÉCU[1], N. ROSSIGNOL[1], C. HABAS[2], A. ARLEO[1];
[1]Sorbonne Univ. - Vision Inst., Paris, France; [2]CHNO des Quinze-Vingts, Paris, France

Abstract: Orienting in space requires active visual exploration and the processing of environmental cues. Visual spatial cues can either be geometric, such as the global shape of the environment, or correspond to local landmarks, such as objects or features independent of the environment's layout. Although the cortical and subcortical structures implicated in spatial coding are well characterized, the neural networks involved in geometry vs. landmark visual cue reliance remain elusive. To address this issue, this study used functional magnetic resonance imaging (fMRI) to differentiate the brain activities that are specifically associated with landmark- and geometry-based navigation. Twenty-five young participants (μ=25.4 years, σ=42.7; 7F) performed a virtual navigation task in the scanner. Participants explored a Y-maze and had to learn the location of a hidden goal. Subjects then had to navigate to the goal from different starting positions throughout the maze in two separate conditions: a landmark

condition, in which reorientation required the processing of three differently-shaped objects; and a geometry condition, in which reorientation required the processing of the environment's shape. Participants performed similarly in both conditions in terms of escape latency, trajectory accuracy, and rate of correct responses. At the cortical level, two distinct cerebral networks were observed. Reorienting based on landmark information was associated with a greater occipital, hippocampal (posterior and anterior parts), and cerebellar involvement as well as with a specific activation of the perirhinal cortex. In contrast, reliance on the geometric shape of the environment elicited a specific activity in the anterior cingulate and frontal cortices. ROI analyses revealed that the dorsal striatal structures were activated in the geometric condition only, whereas the hippocampus had similar activations in the two conditions. The pattern of activity associated with landmark-based reorientation is congruent with the processing of fine-grained spatial information, while the increased frontal and cingulate activities in geometry-based reorientation reflect the task's greater cognitive control requirements. Moreover, in the geometry condition, the co-activation of hippocampal and striatal regions seems to indicate a flexible use of several navigational strategies mediated by frontal regions. These findings show that the type of visual spatial cue available in the environment influences the behavioral strategy and the underlying brain dynamics during spatial navigation.

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Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.05/BB6

Topic: H.02. Human Cognition and Behavior

Support: NSERC Grant 06748

Title: Improving individuals' spatial orientation skills

Authors: *M. A. R. MCLAREN-GRADINARU[1], F. BURLES[2], I. DHILLON[2], A. RETSINAS[2], A. UMILTÀ[1], G. IARIA[1];
[1]Neurosci., [2]Psychology, Univ. of Calgary, Calgary, AB, Canada

Abstract: Healthy individuals vary widely in their ability to find their way around, with some people finding it extremely difficult or nearly impossible to orient in a new surrounding without getting lost. Such difficulty in spatial orientation and navigation seems to be related to the inability of the individuals to efficiently form and make use of a cognitive map, i.e. a mental representation of the environment in which environmental landmarks and their spatial relationships are represented. In this study, we designed a training program in a virtual

environment with the aim of improving the ability of the individuals to orient and navigate by using environmental landmarks. Throughout the training program, we asked participants to travel back and forth between key environmental landmarks until they had built an understanding of where those landmarks resided with respect to one another. This process repeated until they had visited every landmark and learned where each landmark was located with respect to the others. The program consisted of a daily training session of 45 minutes for a total duration of 10 days. Before and after the training program, we measured participants' subjective orientation experience in daily life, and their ability to perform a series of computerized behavioural tasks assessing a variety of spatial orientation skills. We found that following the training program participants improved their ability to form cognitive maps, as well as their subjective experience in their daily life orientation. These preliminary findings could have significant implications for improving orientation skills in individuals affected by topographical disorientation and the elderly population in general.
Funding: NSERC

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Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.06/BB7

Topic: H.02. Human Cognition and Behavior

Support: NSERC 06748

Title: Structural properties of the brain in developmental topographical disorientation

Authors: *J. A. HANNAH, F. BURLES, J. KOHL, K. JELINKOVA, J. PARMAR, G. IARIA; Dept. of Psychology, Univ. of Calgary, Calgary, AB, Canada

Abstract: Developmental Topographical Disorientation (DTD) refers to a lifelong condition in which individuals are unable to orient and navigate in familiar surroundings, despite well preserved general cognitive functioning. Behaviourally, this condition stems from an inability to form a mental representation of the environment (i.e. a cognitive map) that is known to be critical for effective orientation and navigation. To date, however, its structural neurological basis remains largely unknown. In the present study we investigated the volumes and structural integrity of the caudate nucleus (head and body) and the hippocampus (head, body and tail) as these two regions are particularly involved in procedural and non-procedural mechanisms of spatial orientation in humans. We recruited 20 individuals with DTD and 17 control subjects matched for age, gender, handedness and education. The participants were scanned using a 3T

MRI protocol including T1 anatomical imaging and diffusion weighted imaging. Subregions of the hippocampus and caudate nucleus were manually traced using MRIcron. We compared the mean voxel count, fractional anisotropy (FA), and mean diffusivity (MD) of each subregion between DTD and control participants. The results revealed that individuals with DTD tend to have larger hippocampus tails in both hemispheres as compared to controls. We did not detect any other volumetric differences between groups. In terms of structural integrity, the DTD group revealed significantly higher MD in the right caudate nucleus head and significantly higher FA in the right hippocampus head. These findings represent the very first group-based brain structural differences between individuals with DTD and healthy controls and provide a unique opportunity to understand the neurological effects of this developmental condition in the context of neuroplasticity and compensatory cognitive mechanisms adopted in daily life.

Disclosures: **J.A. Hannah:** None. **F. Burles:** None. **J. Kohl:** None. **K. Jelinkova:** None. **J. Parmar:** None. **G. Iaria:** None.

Poster

516. Human Perceptual and Spatial Learning

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Program #/Poster #: 516.07/BB8

Topic: H.02. Human Cognition and Behavior

Support: Canadian Natural Sciences Engineering Research Discovery and Accelerator Grants
James S. McDonnell Foundation Scholar Award
Canada Research Chairs Program

Title: The functional contribution of anterolateral entorhinal cortex to intra-item configural processing

Authors: *J. C. LIANG[1], R. K. OLSEN[2], N. G. Y. SHING[2], N. LADYKA-WOJCIK[1], J. D. RYAN[2], M. D. BARENSE[1];
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Abstract: There is mounting evidence from studies with humans and rodents that subregions of entorhinal cortex (ERC) are functionally distinct. However, there are disparities in the methodologies used, in the anatomical correspondence across species, and even in the operations these ERC subregions are thought to support. Recent work with humans using MRI found that the volume of anterolateral entorhinal cortex (alERC) predicted intra-item configural processing (i.e., the degree to which one processes the spatial arrangement between an object's features, as measured by eyetracking) across individuals. Having established the importance of alERC volume to intra-item configural processing, we conducted a follow-up fMRI study within the

same cohort of older adult men and women to establish whether the activity of alERC tracked intra-item configural processing on an object-to-object basis. Moreover, we asked whether alERC responded uniquely to different forms of intra-item configural novelty. Finally, we examined how decreases in alERC volume over time impaired general configural processing as well as configural novelty detection. We found above chance multivariate decoding of eye position consistent with sensitivity to spatial configurations.

Disclosures: **J.C. Liang:** None. **R.K. Olsen:** None. **N.G.Y. Shing:** None. **N. Ladyka-Wojcik:** None. **J.D. Ryan:** None. **M.D. Barense:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.08/BB9

Topic: H.02. Human Cognition and Behavior

Title: Learning and categorization of objects through haptic exploration

Authors: *K. GAUDER[1], D. GOLDREICH[2];
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Abstract: With haptic exploration—the active manipulation of objects to gather information through touch—the brain can seamlessly integrate features into whole percepts, learning the categorical and statistical structures of the world. The processing that underlies this ability is poorly understood. One way to understand this process is through Bayesian inference—a probability framework for comparing hypotheses as information is gathered. This approach has seen success in vision and audition but has rarely been extended into haptics. Here we compare human performance against that of an optimal Bayesian observer. Participants attempted to categorize a set of 3D-printed polygons from which we defined two novel categories with overlapping feature distributions. These features were the number of sides and the spacing of raised dots on one of the surfaces. In Experiment 1, 45 participants completed 9 blocks of 40 trials in one of three training regimens: 1) single-category exposure followed by testing with corrective feedback, 2) single-category exposure followed by testing without feedback, and 3) no prior exposure, testing with corrective feedback. Each trial, participants gave their best guess for object category and their confidence. All participants demonstrated category learning. Group (3) achieved the best performance. Intriguingly, performance did not asymptote, suggesting that further improvement with additional training is possible. To test this hypothesis, in Experiment 2 we conducted 5 sequential days of testing (45 blocks) using regimen 3. We additionally performed Bayesian statistical analysis to determine which of 4 models best predicted the data from each participant: categorization based on both features (expert), a single feature (raised dot spacing or number of sides), and pure guessing. Preliminary results with 7 participants reveal

that 1) performance does not improve noticeably after the first day of testing, and 2) the number of participants whose behaviour fell consistently (majority of the blocks) into each category were: expert (1), single feature (5), guessing (1). Among the single feature participants, dot spacing was the predominantly attended feature. Three of these participants achieved expert performance on at least 5 blocks. We conclude that most individuals can learn statistical categories serving haptic object classification, but only a minority are able to combine cues at an expert level. Furthermore, performance saturates after just one day of training.

Disclosures: **K. Gauder:** None. **D. Goldreich:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

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Program #/Poster #: 516.09/BB10

Topic: H.02. Human Cognition and Behavior

Title: Exploring emotion-related changes in spatial memory with virtual reality

Authors: C. BUHLER, **E. NYAM-OCHIR**, M. DIAMOND, M. CLAYTON, *J. O. TAYLOR; Behavioral Sci., Utah Valley Univ., Orem, UT

Abstract: Virtual reality (VR) is an increasingly popular and affordable tool used in clinical and research settings. The presentation of aversive visual and auditory stimuli within a virtual environment can elicit changes in autonomic activity and self-reported indices of emotion, a fact that has made VR a popular platform for the gaming industry as well as therapeutic intervention for emotional disorders such as phobia. Despite limitations of using VR as a true real-world analog, it can serve as a valuable tool in research settings. VR environments have good internal validity by controlling for situational noise and nuanced exposure to stimuli. VR also helps to ameliorate some practical and ethical constraints associated with human research such as allowing for exposure to potentially dangerous situations/stimuli, creating large experimental contexts, and the presentation of complex stimuli that would be difficult to create in a typical laboratory setting. As a result, immersive VR environments are used to explore a variety of clinically relevant research questions. In this study, a VR program was developed with two primary goals: (1) modulate anxious and fearful states in participants while navigating a maze, (2) evaluate emotion-related changes in spatial learning and memory. To accomplish these goals, a virtual hedge maze was designed so that participants would first explore the maze with one of three sets of auditory and visual stimuli. The stimulus sets were designed to elicit emotional states along a gradient from anxious to fearful: diffuse, low intensity aversive stimuli were intended to evoke anxiety, whereas discrete, higher intensity aversive stimuli to evoke fear. Subsequent exploration could be conducted in one of the initial conditions, or in the absence of aversive stimuli. A virtual Corsi block test was delivered prior to, between, and after maze trials

as an additional control for stability of spatial memory within the experiment. Stimulus or context related changes in emotional state were assessed via measures of autonomic activity and self-report. Maze spatial memory was assessed via changes in various movement-related factors (e.g., total time, number of errors, time spent at decision points). This design provides a frame work for exploring the interaction between emotional state and memory with easily manipulated contextual and discrete variables.

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Poster

516. Human Perceptual and Spatial Learning

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Program #/Poster #: 516.10/BB11

Topic: H.02. Human Cognition and Behavior

Support: CIHR Grant No. 126105 awarded to MN Rajah
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Title: Individual differences in gray matter of posterior medial structures predict source memory accuracy

Authors: *J. SNYTTE[1], A. ELSHIEKH[4], S. SUBRAMANIAPILLAI[2], S. PASVANIS[5], M. D. BARENSE[6], R. K. OLSEN[7], M. N. RAJAH[3];
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Abstract: A recent model integrating evidence from the dual-process theory of recognition memory (Yonelinas, 2002) and the hierarchical-representational perspective (Murray, Bussey, & Saksida, 2007) has suggested that two anatomically distinct networks support distinct memory and perceptual processes (Ranganath & Ritchey, 2012). According to this model, an anterior-temporal (AT) network supports cognitive processes related to “entities” - this includes memory and perception of words and objects, whereas a posterior-medial (PM) network is critical in establishing and recollecting relational links between items and external contextual information. While there is strong support for this model from functional imaging studies, there is a lack of support and consistency from structural MRI studies. To assess this model from a structural perspective, we tested 25 healthy young individuals on an object-location associative memory task and a feature conjunctive perception task (mean age = 22.00 , SD = 3.64). We obtained gray matter (GM) volume estimates of medial temporal lobe (MTL) regions of interest (ROIs) using a

semi-automated segmentation technique (Olsen et al., 2013; Pipitone et al., 2014). We obtained cortical thickness measurements for the non-MTL ROIs using an automated pipeline (Ad-Dab'bagh et al., 2006; Lerch & Evans, 2005). We then used partial-least-squares regressions to determine which regions were significantly related to latent variables (LV) predicting either associative memory, object recognition, or feature conjunctive perception. Based on the AT-PM model we hypothesized that: (1) GM of PM ROIs, but not AT ROIs, would significantly be correlated to the LV predicting associative memory accuracy and (2) GM of AT ROIs, but not PM ROIs, would be significantly related to the LVs predicting object recognition memory and feature conjunctive perception. Our analyses revealed one LV which significantly predicted 52.38% of the variance in associative memory accuracy. We found that GM in a subset PM regions - medial prefrontal cortex ($p = .0053$, $\beta = .0093$), angular gyrus ($p = .0166$, $\beta = .0112$), precuneus ($p = .0232$, $\beta = .0092$), and posterior hippocampus ($p = .0115$, $\beta = .015$), and GM in a subset of AT regions - temporopolar cortex ($p = .0033$, $\beta = .0142$), and orbitofrontal cortex ($p = .0095$, $\beta = .0127$), were significantly positively correlated with this LV. We did not find an LV that significantly predicted object recognition or feature conjunctive perception. This study provides structural evidence which complements and elaborates on the AT-PM model and further demonstrates how individual differences in GM of specific structures relate to specific memory processes.

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Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.11/BB12

Topic: H.02. Human Cognition and Behavior

Title: Low frequency EEG phase synchronization of cortico-hippocampal communication in human spatial navigation

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Abstract: In addition to the hippocampus (HC) and entorhinal cortex (EC) that are the key brain regions of spatial navigation system, prefrontal cortex (PFC) also plays a significant role in episodic memory related to spatial navigation. Although explicit evidence indicates that these brain areas communicate via oscillatory synchrony, how interbrain communication precisely transmits information and controls the timing of information interaction is still outstanding questions. Here we recruit preoperative epilepsy patients as subjects and allow them to

participate in tabletop navigation task of virtual reality. Meanwhile, we recorded iEEG signals of the deep electrode of the patients during the virtual navigation experiment. By analysing the neural oscillatory signals of local field potential (LFP) in hippocampus, entorhinal cortex and prefrontal cortex, we found that in the coding and retrieval phases of episodic memory in spatial navigation, there was a significant phase synchronization in low-theta (1-3 hz) and theta (4-8 hz) between either hippocampus and entorhinal, and between hippocampus and prefrontal cortex. Such phase synchronization is absent in other frequencies. In addition, we found that the phase synchronization is related to the merits of episodic memory retrieval and navigation ability. Our results reveal the communication mechanism based on neural oscillations in low theta and theta frequency band among hippocampus, entorhinal cortex and prefrontal cortex. The phase synchronization of low frequency (1-8hz) can serve a biological marker of coding and retrieval information in human episodic memory.

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Poster

516. Human Perceptual and Spatial Learning

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Program #/Poster #: 516.12/BB13

Topic: H.02. Human Cognition and Behavior

Support: Novartis Research Grants

Title: Functional connectivity measured with resting state functional magnetic resonance imaging as a biomarker of spatial neglect during recovery rehabilitation period of stroke

Authors: ***T. EBISU**[1], M. FUKUNAGA[2], T. MURASE[3], M. UMEDA[3];
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Abstract: *Background:* Spatial neglect, which prevents stroke patients from acquiring ability of independent daily living, has been reported to be related with change in the network interactions in the brain. However, it is still unknown whether functional connectivity observed with resting state functional MRI (rs-fMRI) can be a useful imaging tool for evaluation of spatial neglect in clinical practice. The goal of this study was to determine if functional connectivity measured with rs-fMRI could be used as a biomarker of spatial neglect during the recovery rehabilitation period after a stroke.*Methods:* The rs-fMRI data of 8 stroke patients and 31 healthy subjects were analyzed by the seed-based method with the Anatomical Automatic Labeling (AAL) template and Data Processing Assistant for Resting-State fMRI (DPARSF). The functional connectivity score (FCS) was defined as the correlation z score of each AAL region with right inferior and

superior parietal lobules (AAL 60, 62, 64, and 66). The neglect measure was determined with the behavioral inattention test (BIT). The relationship between FCS and BIT of stroke patients was examined in the selected regions, where a high absolute value of FCS was revealed in healthy subjects, during the recovery rehabilitation period. *Results:* The FCS between the right inferior parietal lobule (AAL 62) and the pars triangularis of the right inferior frontal gyrus (AAL 14) was significantly correlated with BIT. In addition, the FCSs of these regions in stroke patients with spatial neglect was significantly decreased, compared with those without spatial neglect. Secondly, negative correlation was detected between the right inferior parietal lobule (AAL 62) and the regions related with the default mode network such as the bilateral medial superior frontal gyri (AAL 23, 24, 25, and 26), posterior cingulate gyri (AAL 35 and 36), and hippocampus (AAL 37 and 38) in stroke patients without spatial neglect in contrast to a loss of negative correlation with spatial neglect. Furthermore, positive correlation was detected between the right superior parietal lobule (AAL 60) and the right caudate (AAL 72) in stroke patients with spatial neglect, in contrast to negative correlation without spatial neglect.*Conclusion:* These findings may support the hypothesis that functional connectivity measured with rs-fMRI is a useful tool for evaluation of spatial neglect during the recovery rehabilitation period after stroke.

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Poster

516. Human Perceptual and Spatial Learning

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Topic: H.02. Human Cognition and Behavior

Support: NIH-R01-HD087089
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Eric P. and Evelyn E. Newman fund

Title: Visual perception of joint stiffness from multi-joint limb motion

Authors: *M. E. HUBER[1], A. M. WEST, Jr.[1], C. FOLINUS[1], N. HOGAN[1,2];
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Abstract: Humans have an astonishing ability to extract hidden information from the movements of others. For example, even with only limited kinematic information, humans can distinguish between biological and non-biological motion, identify the age and gender of a human demonstrator, and recognize what action a human demonstrator is performing. It is unknown, however, whether they can also estimate hidden mechanical properties of another's limbs simply by observing their motions. Strictly speaking, identifying an object's mechanical

properties, such as stiffness, requires contact. With only motion information, unambiguous measurements of stiffness are fundamentally impossible as the same limb motion can be generated with an infinite number of stiffness values. However, we found that humans can readily estimate the stiffness of a simulated limb from its motion. In a set of three experiments, we observed that participants linearly increased their rating of arm stiffness as joint stiffness parameters in the arm controller increased. This was remarkable as there was no physical contact with the simulated limb. Moreover, participants had no explicit knowledge of how the simulated arm was controlled. An additional set of three experiments tested whether participants could still estimate joint stiffness if the simulated arm followed the same endpoint paths as in the prior experiments but moved with a non-biological velocity profile. In these experiments, we found no relationship between participants' stiffness rating and simulated joint stiffness. Together, these results suggest that participants likely drew upon prior knowledge of human neuromotor control to successfully map non-trivial changes in multi-joint motion to changes in arm stiffness. Having an internal representation consistent with the behavior of the controller used to drive the simulated arm implies that this control policy competently captures key features of veridical biological control. Finding that humans can extract latent features of neuromotor control from kinematics also provides new insight into how humans interpret the motor actions of others.

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Poster

516. Human Perceptual and Spatial Learning

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Program #/Poster #: 516.14/BB15

Topic: H.02. Human Cognition and Behavior

Support: TOYOTA MOTOR CORPORATION
KAKENHI Grand Number JP18K15341

Title: Bayesian surprise precedes successful memory encoding

Authors: *Y. SHIKAUCHI[1], K. KITAJO[1,2,3];
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Abstract: Although learning and memory are always one of the biggest research fields in neuroscience, it is obscure how these are different and how these are common. In the framework of the Bayesian brain hypothesis, learning is equivalent to an update of an internal generative model. A Bayesian observer summarizes observations as the internal model, and thereby it does not keep the memory of each observation. To relate the Bayesian viewpoint to real information processing involved in memory, we examined the contributions of Bayesian model during

incidental memory encoding to subsequent memory recognition using an auditory recognition task with electroencephalographic (EEG) recordings. We presented twenty-two participants with multiple trains of four tones. Participants were required to respond to each train whether it is an upward tendency or a downward tendency. There were no explicit motivation or instructions to remember any of the tone sets. Immediate after the encoding sessions, an unannounced recognition test was administered. Assuming the Bayesian optimal observer, we computed single-trial information processing that reflects the order of appearance during the encoding sessions. Two model variables, the difference between a prior and a posterior (update) and a negative logarithm of model prediction (surprise), were examined with respect to the relations with memory performance. We found that both variables strongly affected the confidence of the trend judgment in encoding. Moreover, higher surprise during encoding precedes higher recognition performance in recognition test. Additionally, frequency analysis of EEG data from encoding sessions showed that the trials with larger update led to the enhancement of preceding theta power in fronto-parietal regions, compared to those with a smaller update. Our results provide new insight into the relationship between learning and memory; a possible explanation is that the Bayesian perceptual learning partly overlaps with successful memory encoding.

Disclosures: **Y. Shikauchi:** None. **K. Kitajo:** None.

Poster

516. Human Perceptual and Spatial Learning

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Topic: H.02. Human Cognition and Behavior

Support: Intramural Research Program, National Institute of Mental Health (ZIAMH002920)

Title: Identifying distinct functional subdivisions of the anterior temporal lobes

Authors: *S. J. GOTTS, A. S. PERSICHETTI, A. MARTIN;
Lab. of Brain and Cognition, NIMH/NIH, Bethesda, MD

Abstract: The functional role of the anterior aspects of the temporal lobes (ATL) is a contentious issue in cognitive neuroscience. A wide range of functions have been posited in object recognition, language processing, and social cognition. Given the anatomical heterogeneity of this brain region, the ATL almost certainly supports a wide array of cognitive functions. Our goal is to identify functionally distinct regions within the anterior temporal lobes and understand the extent to which each region is involved in specific cognitive functions. We used resting-state fMRI from 88 participants (24 female) and a novel clustering method to identify subdivisions within the ATL, as well as medial temporal lobe structures (amygdala and

hippocampus). Specifically, we calculated the functional connectivity (Pearson correlation of the resting-state time series) between voxels within the ATL (defined as any temporal lobe voxels anterior to y=-35 in Talairach space) and all voxels outside of the temporal lobes. We then thresholded the resultant correlation matrices across a wide range of correlation values, and clustered the group-average matrices using both Infomap and Louvain Modularity. Finally, the identified parcels were required to replicate across halves of the data (44 participants in each half) and across 10 randomized split-half samples. We identified 5 neocortical and 3 medial temporal networks, corresponding to at least 10 functionally distinct parcels in each hemisphere. Hierarchical and K-means clustering revealed that these networks were organized into 4 larger parent networks with specific target profiles outside of the temporal lobe (2 which divided the larger "default-mode" network into language-related versus more executive function regions, 1 related to visual, auditory, and somatosensory processing, and 1 related to high-level visual and memory processing). This information will be used in the next phase of the project to design experimental task manipulations to more precisely dissociate these parcels based on their unique contributions to specific cognitive tasks.

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Poster

516. Human Perceptual and Spatial Learning

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Topic: H.02. Human Cognition and Behavior

Support: Natural Science Foundation of China grant (31230030)

Title: V1 BOLD signal changes associated with orientation learning and transfer at different visual hemispheres

Authors: *D. HU[1], X. XIE[1], C. YU[1], P. ZHANG[2];
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Abstract: Functional neuroimaging of perceptual learning often ignores the transfer issue and focuses on specificity to seek low-level learning mechanisms. However, recent psychophysical evidence shows that not only location and feature specificity can be completely abolished with new training methods like double training, but learning of some basic features such as orientation transfers mostly to new locations. Therefore, perceptual learning involves high-level processing and is in principle transferrable. Here we purposely selected a peripheral orientation discrimination task whose learning is known to show great transfer, and used fMRI to investigate the brain mechanisms underlying both learning and transfer.
23 participants practiced orientation discrimination with a noise grating formed by pixelated

stripes of various widths and spacing at the lower-left or -right quadrant. The reference orientation was tangential to fixation. Five sessions of training improved orientation discrimination at the trained quadrant by 43.2±2.5%, as well as at an untrained contralateral quadrant and orthogonal orientation by 32.5±3.4%. The mean transfer index was 0.76±0.07, indicating great learning transfer.
Two fMRI tests were performed before and after training, following the behavioral tests. Participants performed orientation discrimination in the scanner with stimuli presented at the thresholds of pre- and post-tests, respectively. Independent functional localizers were used to identify the retinotopic ROIs of early visual cortex. The BOLD signals with the trained orientation discrimination task increased by 14.19% in V1 (p=0.00001), 17.78% in V2 (p=0.0006), and 10.64% in V3 (p=0.017) at the trained hemisphere. The BOLD signals with the same task also increased by 11.12% in V1 (p=0.011), 13.23% in V2 (p=0.0095), and 5.70% in V3 (p=0.018) at the untrained hemisphere. Across individuals, the transfer index of V1 BOLD signals was positively correlated with the behavioral transfer index (r=0.46, p=0.031). These learning-associated brain activity changes were not observed when participants performed an untrained frequency discrimination task with the same stimulus.
The cross-hemisphere transfer of orientation learning and the task dependent BOLD signal increases suggest the intrinsic involvement of high-level brain areas in perceptual learning and modulation effects on V1 activities as a consequence. Further analysis will elucidate response changes associated with learning and transfer in high-level and possibly subcortical regions, and the causal connectivity changes between brain areas.

Disclosures: **D. Hu:** None. **X. Xie:** None. **C. Yu:** None. **P. Zhang:** None.

Poster

516. Human Perceptual and Spatial Learning

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Topic: H.02. Human Cognition and Behavior

Support: ARC DP180100670
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ARL W911NF-10-2-0022
ARL W911NF-10-D-0002/TO 0023

Title: Human brain dynamics during navigation with natural walking under different workload conditions in virtual reality by using the mobile brain/body imaging approach

Authors: ***T.-T. N. DO**[1], C.-T. LIN[1], C. A. CORTES[1], A. K. SINGH[1], J. LIU[1], H.-T. CHEN[1], K. GRAMANN[1,2,3];
[1]Fac. of Engin. and Information Technol. (FEIT), Univ. Of Technol. Sydney, Ultimo, Australia;

[2]Psychology and Ergonomics, Berlin Inst. of Technol., Berlin, Germany; [3]Ctr. for Advanced Neurolog. Engin., UCSD, San Diego, CA

Abstract: Spatial navigation is a complex cognitive process based on proprioception, vestibular, and visual cues that are integrated and processed by a wide network of brain areas. The retrosplenial complex (RSC) is an integral part to coordinate and translate between egocentric and allocentric reference frames. Previous works using electroencephalography (EEG) revealed navigation related modulations in different frequency bands in the RSC. However, these studies were based on stationary setups which might not be comparable to the cognitive processes during spatial navigation while naturally walking.

We applied the Mobile Brain/Body Imaging (MoBI) approach to study the human brain dynamics in an ambulatory Virtual Reality (VR) setup. In each trial, the participant was first prompted with one landmark and was instructed to remember the location of the landmark which then disappeared. They then physically navigated paths including two or three turning points. After first navigation phase, participants had to point to the non-visible landmark and subsequently had to memorize a series of letters to indicate, after a short rehearsal interval, whether a target letter was part of the learned set or not. Then, participants navigated a second path including two or three turns while memorizing the positive set and the landmark location. At the end of the second navigation phase, participant again pointed to the landmark.

Seventeen participants (two females) participated in the experiment. The neurophysiological data was collected with a wireless 64-channels EEG system (LiveAmps, Brain Products). EEG data was analyzed using Independent Component Analysis (AMICA) with subsequent source reconstruction of brain components using equivalent dipole modelling. The closest brain region of interest (ROI) to the RSC Talairach location (x=0, y = -45, z = 10) was found by using repeated k-means methods (n = 10000 repeated times) using Independent Components (ICs) properties.

In this study, the results of event-related spectral permutation (ERSP) at RSC showed an upper alpha band (10-12Hz) decrease when the participant actively explored the virtual environment, which concurred with previous stationary experiment using a 2D display. Moreover, there was a delta (1-4 Hz) and theta (4-7 Hz) band ERSP increase after each turning points where participant changed their orientation, which indicates RSC may coordinate with other brain areas like hippocampus to update position of landmarks. In addition, we found that there was a significant decrease in upper alpha and low beta (12.5-15 Hz) bands at RSC in second walk condition, reflecting an influence of the workload to RSC activity.

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Poster

516. Human Perceptual and Spatial Learning

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Program #/Poster #: 516.18/BB19

Topic: H.02. Human Cognition and Behavior

Support: NRF-2017S1A5A2A01024313

Title: Visual perceptual learning does not enhance metacognitive efficiency

Authors: *D. KWON, Y. SHIN, D.-J. YI;
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Abstract: Metacognition is knowing about what we know and what we don't know. In an experimental setting, metacognition is measured through participants' self-reported ratings on how confident they are about their responses in a task. Quantitative levels of metacognition is calculated through metacognitive sensitivity (meta-d' or type 2 d'), which is derived from the sensitivity (d', type 1 d', or first-order performance) representing a participant's performance in a task (Maniscalco & Lau, 2012). Metacognitive efficiency is defined as each individual's metacognitive ability (measured as a ratio of meta-d' to d') under a level of task difficulty controlled across all participants. Metacognitive efficiency is known to vary across different individuals and develops almost exclusively throughout adolescence but rarely changes throughout adulthood (Weil et al., 2013). Generally during visual perceptual learning, enhancement of participants' task performance (first-order performance) shows a specificity that heavily skews towards a trained direction or location. Our current study investigated changes in metacognitive efficiency during visual perceptual learning. Participants were asked to rate confidence levels on their responses on a 4-point scale after identifying the visual field with dots in a coherent motion, as opposed to the visual field containing dots in random motion—each of which was presented randomly in either the left or right visual field. In the test sessions conducted on the first and last days of the five-day-long study, motion of dots were presented in two different directions. However, in the training sessions on the second, third and fourth days of the study, motion of dots were presented in only one direction. We analyzed the data collected across all five days to conduct a side-by-side comparison between the changes in performance and metacognitive efficiency for the trained direction and untrained direction. Not unlike the findings of previous studies, performance increased for the trained direction but not for the untrained direction. More importantly, our results showed that metacognitive efficiency remained constant regardless of training. Our results suggest that metacognitive efficiency is unaffected by visual perceptual learning unlike first-order performance. * This work was supported by the Ministry of Education of the Republic of Korea and the National Research Foundation of Korea(NRF-2017S1A5A2A01024313)

Disclosures: **D. Kwon:** None. **Y. Shin:** None. **D. Yi:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.19/BB20

Topic: H.02. Human Cognition and Behavior

Support: Hong Kong Research Grants Council, GRF 17407914

Title: Event similarity biases perceived spatial distance

Authors: ***X. XING**, J. SAUNDERS;
The Univ. of Hong Kong, Hong Kong, Hong Kong

Abstract: The hippocampus is known to be involved in both episodic memory and spatial navigation. If representing space is part of the more general function of encoding episodic memory of events, the encoding of places and events might be intermixed. Non-spatial properties that determine the association between events might therefore influence spatial judgments. We attempted to manipulate distance in mental representation of places though similarity of events at the places. In virtual reality, subjects learned a map constructed with pairs of houses at same distance in space but with either the same event or different events. The events were either standing on a stone to trigger presentation of name of a blue house, or bypassing a wall blocking the view of name of a red house. Distance in mental representation was measured by priming in a recognition task. When a house name was preceded by name of a similar house, it was expected to be primed and therefore recognized faster than when preceded by name of a different house. Distance in space was measured by estimating distances between houses, and by reconstructing the map. The estimated spatial distance between similar houses was expected to be shorter than for different houses. We observed an overall tendency toward judging houses with the same events as closer in space, with some individual differences in the direction of bias. We further found that distance in mental representation, as measured by recognition priming, was a predictor of judged spatial distances. Our results demonstrate that similarity of events at places can cause places to appear closer in space. This is consistent with the idea that common mechanisms underlie the representation of space and episodic memory.

Disclosures: **X. Xing:** None. **J. Saunders:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.20/BB21

Topic: H.02. Human Cognition and Behavior

Title: EEG-derived changes in brain activation and network connectivity in corporate employees due to brain training

Authors: *S. CHELIAN, S. L. MILLER, W. MCBURNETT, A. A. KRUSE;
Platypus Inst., San Diego, CA

Abstract: Employee volunteers (n=21) underwent a neurocognitive training program - which consisted of an initial assessment, a six week “boost” or intervention period, and then a re-assessment to track the progress of each participant. Assessments consisted of the DANA Standard battery along with synchronized EEG recording. For brain training, subjects were given the goal of completing twenty 30-minute training sessions over a 6-week period using BrainHQ. A median split of the group created two training groups: a long-training group that averaged 30 hours of total training during the training period; and a short-training group that averaged 7 hours of training. Whereas previous work focused on changes in behavioral data, here we report on EEG-derived changes in brain activation and network connectivity. EEG analysis included measurements of band power at electrodes and brain sources as well as information flow between brain sources. Results show the task-specific recruitment of brain regions as well as providing observations into mechanisms of neuroplasticity. Insights from this study could lead to new tools and approaches to enhance the neurocognitive performance of elite performers in a variety of domains.

Disclosures: S. Chelian: None. **S.L. Miller:** None. **W. McBurnett:** None. **A.A. Kruse:** None.

Poster

516. Human Perceptual and Spatial Learning

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 516.21/BB22

Topic: H.02. Human Cognition and Behavior

Title: Dynamics and maintenance of cognitive training effects: Analysis of a massive observational dataset

Authors: *R. J. SCHAFER, N. F. NG, A. M. OSMAN;
Lumos Labs, San Francisco, CA

Abstract: Computerized cognitive training, including programs offered via online "brain training" websites and apps, has been the focus of numerous studies over the past decade. While randomized controlled trials have begun to shed light on the efficacy of such training programs, many open questions remain, such as the form of the "dose-response" relationship between brain training and cognitive outcomes, and the extent to which training effects are maintained over time. To address these questions, we analyzed a large, observational dataset of nearly 750,000 individuals who underwent Lumosity online brain training and were assessed with the NeuroCognitive Performance Test (NCPT) at one or more time points separated by several months. Individuals spanned a wide range of ages (13 to 90, median of 46) and educational levels. For all demographic groups examined, we found a consistent, positive relationship between the amount of Lumosity training and improvements on the NCPT from the 1st to 2nd time point. The form of this dose-response function - both the rate of improvement and maximal (asymptotic) improvement - differed across cognitive domains assessed by the NCPT. Examination of the NCPT at the third time point found that improvements in cognitive performance were maintained for months after training with only modest decay. Moreover, additional training between the 2nd and 3rd assessments was associated with small but significant improvement beyond the original training effects.

Disclosures: R.J. Schafer: A. Employment/Salary (full or part-time):; Lumos Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs. **N.F. Ng:** A. Employment/Salary (full or part-time):; Lumos Labs. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Lumos Labs. **A.M. Osman:** A. Employment/Salary (full or part-time):; Lumos Labs.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.01/BB23

Topic: H.02. Human Cognition and Behavior

Support: R01MH104588

Title: The effect of stimulus predictability on cerebro-cerebellar verbal working memory processing: An fMRI study

Authors: *Y.-S. SHEU, Y. LIANG, J. E. DESMOND;
Dept. of Neurol., The Johns Hopkins Univ. Sch. of Med., Baltimore, MD

Abstract: Anticipating forthcoming situations supports efficient and appropriate goal-directed behavior. In the cognitive domain, performance can be boosted by providing valid cues in advance (e.g. pre-cueing task set), or by incidental learning of the statistical regularities that specify the upcoming characteristics of a task (e.g. sequence learning task). In the literature of motor control, an influential theory of cerebellar function posits that the cerebellum makes prediction of the sensory consequences of a movement through an internal forward model. More recently, some investigators have argued that prediction may be a unifying cerebellar function that can be extended to non-motor domains, such as working memory and language. Therefore, in the current study, we used functional magnetic resonance imaging (fMRI) and a modified version of Sternberg verbal working memory task to investigate the cerebellar contributions of self-generated prediction to verbal working memory processing. Seventeen healthy participants were asked to encode a 6-letter sequence, and to covertly rehearse the letters in sync with the guided symbol on the screen. Because the rehearsal is guided, participants can easily predict the identity of the next correct letter in the sequence. We found participants responded faster to the probe letter by about 133 msec when the probe appeared as a match (i.e. predicted stimulus) compared to a non-match (i.e. unpredicted stimulus). Furthermore, the neuroimaging data showed both the match and non-match trails activated a similar fronto-parietal network subserving the neuronal substrates of working memory. Most critically, less activity was found in this fronto-parietal network as well as in right cerebellum for the match trials compared to the non-match trials. Therefore, our results demonstrate that the human brain spontaneously anticipates forthcoming sensory stimulus which allows predictable stimuli to be processed faster and require less neural activation. We also provide additional evidence that the cerebellum plays a function role in prediction by facilitating verbal working memory processing.

Disclosures: **Y. Sheu:** None. **Y. Liang:** None. **J.E. Desmond:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.02/BB24

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH112206

Title: Decoding the temporal dynamics of working memory with recurrent neural networks

Authors: *S. GOLDSTEIN[1], Z. HU[1], M. DING[2];
[1]Univ. of Florida, Gainesville, FL; [2]Univ. Florida, Gainesville, FL

Abstract: Information encoding, retention and retrieval are distinct stages of working memory (WM). Within each stage neural representations of WM undergo dynamic transformation.

Previous applications of machine learning to EEG data recorded during WM have focused on decoding spatial patterns at each instant of time. To what extent information is represented in both spatial and temporal patterns of neural activity remains to be understood. In this study, we decoded working memory load by focusing on spatiotemporal EEG dynamics using recurrent neural networks incorporating long short term memory (LSTM). High density EEG (128-channel) were recorded from twenty subjects performing a Sternberg verbal working memory task. On each trial, a memory array containing either 2, 4 or 6 letters (load 2, load 4 and load 6) was presented for 2000 ms (encoding period). A time period of 3000 ms (retention period) followed the offset of the cue memory array. At the end of the retention period, a probe letter was displayed for 1000 ms (retrieval period), and subjects responded with a button press to indicate whether this letter was contained in the memory array. Following EEG preprocessing, LSTM networks were trained to decode between load 2 and load 6 during retention. There were three findings. First, during the retention period, the decoding accuracy increased with increase in the length of the 128 EEG time series that were inputted into the LSTM, reaching a plateaued decoding accuracy of ~66% when the length of the time series reached ~800ms. Second, the plateaued decoding accuracy in individuals with higher working memory capacity (WMC) is higher than that in individuals with low WMC. Third, after randomly shuffling the time index of the EEG time series, the plateaued decoding accuracy is lower than that of the originally ordered time series, but remains higher than the decoding accuracy from spatial patterns alone. These results suggest that during WM retention, WM information is encoded in both the spatial and temporal dynamics of neural activity, and this is particularly so in individuals with stronger working memory function.

Disclosures: **S. Goldstein:** None. **Z. Hu:** None. **M. Ding:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.03/BB25

Topic: H.02. Human Cognition and Behavior

Title: Single-trial contralateral delay activity also reflects item encoding precision

Authors: *C. MERKEL[1], J.-M. HOPF[1,2], M. A. SCHOENFELD[1,2,3];
[1]Otto-von-Guericke Univ., Magdeburg, Germany; [2]Leibniz Inst. for Neurobio., Magdeburg, Germany; [3]Kliniken Schmieder, Heidelberg, Germany

Abstract: The classical slotmodel of visual working memory (VMW) predicts that a global resource is distributed equally amongst the relevant encoded items. Currently it is debated whether items can be prioritized by assignment to bigger chunks of VWM. Previous work has shown, that enhanced encoding of relevant items translates to a better subsequent recall

precision. The current study uses the contralateral delay activity (CDA) as a continuous measure for single item encoding and quantifies the CDA amplitude associated with VWM resources assigned to individual encoded items. In a delayed precision estimation task, subjects are required to remember the orientation of two bar stimuli, presented in succession (in each encoding phase two bars are presented bilaterally, while subjects attend to either the left or the right hemifield). Subsequently, the orientation of either the first or second orientation has to be recalled using a dial. Consistent with previous reports general CDA amplitude increases were observed for the second item subsequently stored in VWM. Interestingly, the single-trial CDA amplitudes related to the first and second item correlated with the precision of recall for that individual item. The CDA amplitude therefore not only seems to reflect the encoding of an item but also the accuracy of encoding of the representation. Furthermore, the data suggests at least a partial independence of the precision of recall of the first item from the CDA amplitude associated with the second item and vice versa. These results provide support to a variable resource model of VWM.

Disclosures: C. Merkel: None. **J. Hopf:** None. **M.A. Schoenfeld:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.04/BB26

Topic: H.02. Human Cognition and Behavior

Title: The temporal dynamics of working memory: Persistent interactions with perception

Authors: *C. TENG, S. KAPLAN, D. KRAVITZ;
George Washington Univ., Washington, DC

Abstract: The ability to briefly maintain information in working memory (WM) is crucial for a variety of complex cognitive functions, but its neural substrate remains under debate. The classic view is that information is encoded within the posterior sensory cortices but then recoded and maintained in the fronto-parietal network (e.g. Goldman-Rakic, 1995; Xu, 2017). Alternatively, the sensory recruitment model (e.g. D'Esposito & Postle, 2015) posits that WM content is maintained within the sensory regions themselves. To address the controversy, we tested two contrastive hypotheses. First, if WM is maintained in the sensory cortices, there should be bidirectional interference between WM and perception defined by the known tuning curves in these areas for the maintained features. Second, if the WM representation is held in the sensory cortices, its strength should decay across time causing less interference on perception but being more strongly interfered with by perception. If information is being recoded outside of the sensory cortices then both forms of interference should reduce with time.
In Experiment 1 participants (N = 120) performed a color or orientation discrimination task

while holding a color or orientation in mind. The relationship between the WM and the discrimination stimuli were manipulated such that the maintained item was either between the two discrimination stimuli (middle) or to one side (side). As predicted, the item in WM interfered with perception, drawing the discrimination stimuli towards itself and creating worse discrimination thresholds in the middle than the side condition. In turn, the WM report was distorted by perceiving the discrimination stimuli, resulting in a strong bias in the side condition. This effect held for both orientation and color when the same feature was relevant for both the WM and discrimination tasks, but not when the features were different across the tasks despite identical stimulus displays. Thus, the contents of WM both alter and are altered by ongoing perception.
Experiment 2 (N = 150) used the same design but varied the interval between the WM encoding and the discrimination task between 100ms to 4s to map out the temporal dynamics of WM. We found that WM significantly impacted the discrimination thresholds even at the longest delays. Further, while the strength of WM interference on perception decayed across time, the impact from perception on WM increased, contrary to the predictions of the recoding account. Overall, these results demonstrate that WM content is represented in the sensory cortices even for delays of up to 4s and directly interacts with concurrent perception at fundamental stages of visual processing.

Disclosures: **C. Teng:** None. **S. Kaplan:** None. **D. Kravitz:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.05/BB27

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH087214
ONR N00014-15-1-2790
F32 MH115597

Title: Pupillary signatures of attention and working memory fluctuations

Authors: *P. A. KEENE, M. T. DEBETTENCOURT, E. AWH, E. K. VOGEL;
Univ. of Chicago, Chicago, IL

Abstract: Attention and working memory performance constantly fluctuate. Attention fluctuations have been measured behaviorally using response time (RT) in sustained attention tasks. In these tasks, attention fluctuates as does general task engagement, but attention fluctuations are specifically correlated with the number of items held in working memory. We were interested in how, pupil diameter, a putative signal of arousal, related to attention and

working memory performance. In a series of experiments, we sought to investigate whether attention and working memory fluctuations elicited corresponding and concurrent fluctuations in pupil diameter. We designed an experiment that interleaved two established tasks: a sustained attention to response task and a whole-report working memory task. Participants viewed a stream of multi-item shape displays. The attention task was to monitor the shapes of the displays (circles or squares). The working memory task was to occasionally report the color of each shape from the preceding display, after a blank delay screen. We examined how RT and pupil diameter related to the fluctuations of performance on the hybrid attention and working memory task. In Experiment 1, RT (our operationalization of attentional state) covaried with both pupil diameter and working memory performance. In Experiment 2, we modified our attention task to investigate whether pupil diameter could track covert cognitive fluctuations, even without concurrent response demands. Participants completed a modified sustained attention task where they responded only to infrequent target trials. We found that RT to those targets covaried with pupil diameter and working memory performance. In both of these studies we also observed critical differences between RT and pupil diameter, suggesting they were not redundant indices. These results provide further insight into the relationship between cognitive processes and their concurrent fluctuations.

Disclosures: P.A. Keene: None. **M.T. deBettencourt:** None. **E. Awh:** None. **E.K. Vogel:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.06/BB28

Topic: H.02. Human Cognition and Behavior

Support: ZIAMH002798

Title: Threat of shock influences parietal bold responses during a visual short-term memory task

Authors: *N. L. B. BALDERSTON, M. GOODWIN, A. BEALE, M. ERNST, C. GRILLON; NIH, Bethesda, MD

Abstract: Hypervigilance, abnormal orienting to environmental stimuli, is shared across anxiety disorders. This symptom is reflected in the attention biases seen in both clinical anxiety and healthy volunteer models of high state anxiety. Our previous work has shown increased cortical excitability and global brain connectivity in regions of the parietal cortex important for orienting. Based on these results, we hypothesized that threat would also impact orienting and memory performance during a visual short-term memory (VSTM) task. On each trial of the VSTM task, subjects saw an arrow pointing either left or right. Then, an array of squares flashed for 150 ms

on both sides of the screen. Squares differed in terms of color, location, and orientation. Participants were instructed to attend to the squares signaled by the arrow direction, and to ignore the contralateral squares. Next a target square was shown, and subjects made a forced-choice (match vs. mismatch) button press. To manipulate load, we varied the number of ipsilateral squares (2 vs. 4). To manipulate distractor salience, we varied the number of contralateral squares (2 vs. 4). Trials took place during periods of safety and threat of unpredictable shock, BOLD responses were recorded throughout. We extracted BOLD responses to the cue and the square array, and performed ANOVAs on the cue/array-evoked BOLD responses. For the cue-evoked responses, we found a bilateral parietal cluster that responded more toward right-pointing cues during threat. For the array-evoked responses, we found a similar left parietal cluster that responded more during threat when attention was focused to the right, but only when target load and distractor load were congruent. These results suggest that threat impacts attention orienting, and that this effect can influence the neural processing mediating visual short-term memory. These results are consistent with our previous work showing enhanced parietal excitability during threat of shock and offer a mechanistic explanation for the attentional biases and hypervigilance observed in anxiety patients. These results also support the idea that noninvasive neuromodulation targeting the parietal cortex may be a fruitful avenue to treat these symptoms.

Disclosures: N.L.B. Balderston: None. **M. Goodwin:** None. **A. Beale:** None. **M. Ernst:** None. **C. Grillon:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.07/BB29

Topic: H.02. Human Cognition and Behavior

Title: Brain networks communicate through theta oscillations to encode high load in a visuospatial working memory task: An EEG connectivity study

Authors: *S. MUTHUKRISHNAN, S. SONI, R. SHARMA;
Physiol., All India Inst. of Med. Sci., New Delhi, India

Abstract: The encoding of visuospatial information is the foremost and indispensable step which determines the outcome in visuospatial working memory (VSWM) task. It is considered to play a crucial role in limiting our ability to attend and process only 3-5 integrated items of information. Despite its importance in determining VSWM performance, the neural mechanisms underlying VSWM encoding have not been clearly differentiated from those involved during VSWM retention, manipulation and/or retrieval. The high temporal resolution of electroencephalography (EEG) and improved spatial resolution with dense array data acquisition makes it an ideal tool to

study the dynamics in the functional brain connectivity during a cognitive task. In the present study, the changes in the functional brain connectivity due to memory load during VSWM encoding were studied using 128-channel EEG. Lagged linear coherence (LagR) was computed between 84 regions of interest (ROIs) defined according to the Brodmann areas for seven EEG frequency bands: delta (2-4 Hz), theta (4-8 Hz), alpha 1 (8-10.5 Hz), alpha 2 (10.5-13 Hz), beta 1 (13-20 Hz), beta 2 (20-30 Hz), and gamma (30-45 Hz). Interestingly, out of seven EEG frequency bands investigated in the current study, LagR of only theta band varied significantly in thirteen brain connections due to memory load during VSWM encoding. LagR of theta band increased significantly at high memory load when compared to low memory load in twelve brain connections with the maximum change observed between right cuneus and right middle temporal gyrus (Cohen's $d = 0.836$), indicating the integration of brain processes to confront the increase in memory demands. Theta LagR decreased significantly between left postcentral gyrus and right precentral gyrus at high memory load as compared to low memory load, which might have a role for sustaining attention during encoding. Change in the LagR values due to memory load between fusiform gyrus and lingual gyrus in the right hemisphere had a positive correlation ($r = 0.464$, $p = 0.003$) with the error rate, signifying the crucial role played by these two regions in predicting the performance. The current study has not only identified the neural connections that are responsible for the formation of working memory traces during VSWM encoding, but also support the notion that encoding is a rate-limiting process underlying our memory capacity limit.

Disclosures: S. Muthukrishnan: None. **S. Soni:** None. **R. Sharma:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.08/BB30

Topic: H.02. Human Cognition and Behavior

Support: NIH R01EY028746

Title: Reconstructing working memory swap errors with fMRI data

Authors: *R. MALLETT, J. A. LEWIS-PEACOCK;
Psychology, The Univ. of Texas At Austin, Austin, TX

Abstract: Maintenance and manipulation of information in working memory is essential to completing short-term behavioral goals. Working memory performance begins to decline systematically as set size (retention demand) increases beyond capacity limitations. While it is clear that working memory failures occur, the mechanisms by which these failures occur is still under debate. For years, behavioral modeling has proposed two distinct types of response errors that underlie most working memory failures: random guesses and item swap errors. Guesses can

occur when memory information is degraded or inaccessible at the time of test. Swaps (responding as if a different memory item was being probed) likely arise from a contextual binding error that manifests at some point during encoding, retention, or at test. While response modeling can identify potential swap errors, this approach alone cannot explain why they occur. Here, we combined fMRI pattern analysis and response modeling to evaluate the source of swap errors. We designed a visual working memory task to induce a high proportion of swap errors ($\geq$20% of trials). After the encoding of six colored circles at different spatial locations ($\geq$45° apart along a circumference), a centrally presented retrospective cue indicated the color of the item whose location would be tested after a 12-sec delay period using delayed estimation. Participants were prescreened for high swap rates with a single behavioral session. We then collected fMRI data while high-swap participants (N=3) repeated the experiment in the scanner. Trials were binned post-hoc into correct, swap, and guess trials using single-trial mixture model estimates (Schneegans & Bays, 2016). Using an inverted encoding model to project fMRI data back into stimulus space (here, spatial location), we attempted to reconstruct representations of the cued memory location and also non-cued locations on each trial. Corroborating recent fMRI work with smaller working memory set sizes (Sprague et al., 2014, 2016), we show that on correct trials, delay-period activity in early visual areas contains information about the memory target. Notably, we extend this work by showing that on swap error trials, delay-period activity contains information about the swapped non-target location, rather than the memory target. These preliminary results provide neuroimaging support that swap errors in visual working memory arise from early binding failures that perpetuate throughout the retention interval.

Disclosures: R. Mallett: None. **J.A. Lewis-Peacock:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

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Program #/Poster #: 517.09/BB31

Topic: H.02. Human Cognition and Behavior

Support: CIHR, IDRC, ISF and Azrieli Foundation grant 2425/15

Title: Solving the conundrum of working memory training - from manipulation based on dorsal circuitry to strategy based on ventral representations

Authors: *T. MALINOVITCH[1], P. ALBOUY[2,3], R. J. ZATORRE[2,3], M. AHISSAR[1];
[1]Edmond and Lily Safra Ctr. for Brain Sci., Hebrew Univ. of Jerusalem, Jerusalem, Israel; [2]Cognitive Neurosci., Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada; [3]Intl. Lab. for Brain, Music and Sound Res. (BRAMS), Montreal, QC, Canada

Abstract: Training with working memory (WM) tasks yields major improvement. Surprisingly, the question of what is actually learned has not been studied yet. We examined it using two WM tasks: spatial N-back and a novel, extremely challenging task. Since N-back training does not improve performance in other tasks (Jakoby et al., 2019), we hypothesized that participants do not increase their general WM capacity, but instead develop a task-specific strategy that boosts their performance. We derived an effective strategy which relies on minimal changes in the order of items to be remembered, as opposed to the naïve strategy, which requires re-ordering all items in memory. We explicitly taught this strategy to 14 participants and compared their performance before and after instructions to other 14 participants, who trained on the task for 40 sessions with no strategy instruction. With instruction, participants achieved within 2 sessions the same amount of improvement observed after 25-40 training sessions. Importantly, questions presented to the trained group suggested that they used the same strategy, but it took them longer to find.To test the generality of this result we designed a new auditory WM task, where the required manipulation for a trial is given only after the stimuli (sequences of pure tones). 14 participants were trained on this task, and an active control group of 14 participants was trained on a complex perceptual task. Both groups were scanned before and after training while performing each task, using fMRI. Following 40 training sessions, most participants in both groups achieved major improvement in the trained task with no transfer to other tasks. Using a combination of self-reports and data analysis, we discovered that in the WM group, successful learners implicitly developed a surprising strategy. Rather than performing the required manipulation, they learned to efficiently detect one salient tone and assess the expected outcome of the whole sequence. fMRI data revealed a shift in activation patterns: pre-training scans showed activations in dorsal fronto-parietal circuits (for manipulation vs. retention-only contrast), while post-training scans showed an increase in activations in ventral regions along the temporal lobe, associated with domain-specific pitch sequence processing. We propose a novel explanation for the improvement found in WM training studies: during training, efficient learners do not increase their WM capacity as previously claimed. Instead, they develop a strategy that requires fewer manipulations (implemented by fronto-parietal networks) based on the perceptual features of the task (processed in ventral-temporal regions).

Disclosures: **T. Malinovitch:** None. **P. Albouy:** None. **R.J. Zatorre:** None. **M. Ahissar:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

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Program #/Poster #: 517.10/BB32

Topic: H.02. Human Cognition and Behavior

Support: NMSS Grant PP2183

Title: Connectome-based predictive modeling of working memory from resting-state functional connectivity in people with multiple sclerosis

Authors: *A. J. R. SHANKAR, H. R. MANGLANI, S. FOUNTAIN-ZARAGOZA, D. G. EVANS, R. S. PRAKASH;
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Abstract: Previous work associating functional connectivity with behavior has described the consequences of neuronal damage in people with multiple sclerosis (PwMS), including the impairment of working memory systems that underlie complex cognitive functions and are critical for preserved quality of life. Methods to date have been largely correlative in nature, and as such, resting-state functional connectivity (Rs-FC) has yet to be used to accurately predict working memory in PwMS, limiting its potential use as a clinical tool. Connectome-based predictive modeling (CPM; Rosenberg et al., 2016; Shen et al., 2017) is a data-driven technique capable of identifying brain-behavior relationships as well as creating predictive models of behavioral performance from whole-brain functional connectivity. Here, we built two distinct CPMs of working memory using Rs-FC patterns from 27 PwMS (mean age 45.81 ±7.36) to predict performance on the Paced Visual Serial Addition Task (PVSAT) and the WAIS-IV Working Memory Index (WMI), respectively. Using a leave-one-out cross validation procedure, both CPMs successfully predicted working memory performance (correlation between predicted and observed scores: PVSAT: r=.56, p=.003; WMI: r =.51, p=.007), which indicates that the CPM methodology is both sensitive to brain-behavior relationships in PwMS and can create predictive models of working memory solely from Rs-FC. Additionally, we differentiated between the functional connections positively correlated with performance scores (a high-WM network) and those negatively correlated with performance scores (a low-WM network). We found the low-WM networks of both models to be particularly important for predictive power (correlation between predicted/observed scores: PVSAT_low: r=.65, p< .001; WMI_low:r=.51, p=.007), suggesting that certain increases in functional connectivity at rest may be detrimental to working memory performance or indicative of maladaptive firing. As a sanity check for the potential influence of head motion, we also trained a CPM on mean framewise displacement from Rs-FC, which yielded no prediction of head motion (r=.02,p=.936), indicating that our models appear to be unconfounded by such motion.Therefore, our current results support the use of the CPM method as a powerful technique for the prediction of working memory ability in PwMS and suggest the functional connections found in rest are promising indicators of higher-order cognitive function in this population.

Disclosures: A.J.R. Shankar: None. **H.R. Manglani:** None. **S. Fountain-Zaragoza:** None. **D.G. Evans:** None. **R.S. Prakash:** 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.; Funding from NIH and NMSS. Other; Sanofi Genzyme (speaking honoraria).

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.11/BB33

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH087214
ONR N00014-15-1-2790

Title: Distractor suppression in visual working memory

Authors: *L. L. CHAI[1], N. HAKIM[1], T. FELDMANN-WUSTEFELD[2], E. K. VOGEL[1];
[1]Univ. of Chicago, Chicago, IL; [2]Univ. of Southampton, Southampton, United Kingdom

Abstract: Working memory (WM) is a limited capacity system that actively maintains information. Due to its limited capacity, efficient processing of incoming information is necessary. This process relies on filtering and enhancing relevant information and suppressing irrelevant information. Here, we used event-related potentials to investigate suppression of irrelevant information during a WM task. We used the Distractor Positivity (Pd) to track the suppression of irrelevant information in WM. In the first experiment (n=20), participants performed a change detection task for color square arrays presented along the vertical midline. On 50% of trials, we presented task-irrelevant distractors at lateral positions after three different intervals relative to the onset of the memoranda that reflect different moments at which distractors may impact the processing of the targets: initial selection and perceptual encoding (0 ms); WM consolidation (325 ms); and WM maintenance (650 ms). We observed a significant Pd to the lateral distractors presented during each of these periods that was comparable in amplitude for each condition. Thus, these finding suggest that the suppression reflected by the Pd can be deployed during the encoding and maintenance periods of WM. Notably, these results provide initial evidence that the Pd can be observed under conditions in which the targets and distractors are presented separately in time. In the second experiment (n=20), we manipulated the probability of distractor onsets (33% vs 66%) to examine whether top-down expectations modulate the amount of suppression observed to the distractors. This experiment was identical to the 650ms condition of experiment 1, but with separate blocks of either low probability distractors (33%) or high probability distractors (66%). Both conditions generated a significant Pd component. However, when participants did not expect distractors (33% condition), the Pd was significantly larger than when distractors were expected (66% condition). This suggests that when participants expect to be distracted, less suppression may be needed to minimize the impact of distractors on performance; a pattern supported by our behavioral results in which less interruption cost in accuracy was observed for the high probability condition. Together, the results from these experiments show that active suppression of distractors can occur even after

WM representations have been stored and maintained, and that observer expectations can modulate the amount of suppression applied to irrelevant information.

Disclosures: L.L. Chai: None. **N. Hakim:** None. **T. Feldmann-Wustefeld:** None. **E.K. Vogel:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.12/BB34

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH064498

Title: Representing location versus temporal context in visual working memory

Authors: *J. M. FULVIO, B. R. POSTLE;
Psychology & Psychiatry, Univ. of Wisconsin - Madison, Madison, WI

Abstract: Successful performance on working memory tasks often requires encoding of an item's context (e.g., where or when it was presented) in addition to its identity. Recent work from our lab suggests that elevated delay-period activity in parietal cortex may be more sensitive to demands on context-binding than on stimulus representation per se. The present study investigated the effects of varying context-binding demands along two dimensions: high vs. low, and location vs. ordinal position. Healthy young adult humans (male and female) were scanned with fMRI during trials that began with the sequential presentation (500 ms, 250 ms ISI) of three oriented-grating samples at different locations, followed by an 8-second delay, followed by a recognition probe that appeared at one of the three sample locations with a superimposed digit ("1", "2", or "3"). A pretrial instruction cue indicated whether subjects were to respond to the probed location, the probed ordinal position, or to ignore context (i.e., "does probed orientation correspond to any of the three samples?"). Multivariate pattern analysis (MVPA) of context-binding requirements ("high" (location-cued + order-cued) versus "low" (ignore context)) revealed strong sensitivity to context binding at sample and at probe - but not during the delay - in occipital and parietal areas. Additionally, delay-period signal in parietal cortex was higher during high context-binding trials. Within occipital and parietal cortex, MVPA could not discriminate location-cued from order-cued trials during delay and probe. Next, inverted encoding modeling (IEM) was used to assess the neural representation of sample and probe location at response as a function of context. In occipital cortex, the neural representation of the probed location was stronger on location than on order and ignore-context trials, suggesting sensitivity of contextual information to attentional control. However, the neural representation of the location of the invalidly probed sample (i.e., of the digit-cued item on location trials and of

the location-cued item on order trials) was also active.Thus, although the strength of the representation of context is sensitive to strategic factors, context-binding may nevertheless be an obligatory component of working memory.

Disclosures: **J.M. Fulvio:** None. **B.R. Postle:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.13/BB35

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant MH064498

Title: Prior knowledge shapes the neural dynamics of mnemonic and response-related representations in visual working memory

Authors: *Q. YU, B. POSTLE;
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Abstract: Although humans can maintain mental representations of visual information with relatively high precision, their memory performance is not perfect. Previous behavioral studies have demonstrated that responses on tests of working memory for orientations or colors can be strongly biased toward several stable attractors (or priors) in people's long-term representation of orientation/color space, even if memory samples were drawn from a uniform distribution. The neural bases of these biases, however, remain poorly understood. We explored this question by acquiring fMRI while participants performed a delayed recall task of visual orientations. Samples were oriented gratings embedded in noise with different levels of contrast: high-contrast (60%), low-contrast (10%), and 0%-contrast (i.e., a noise patch without visible orientation). On each trial, participants viewed one memory sample, presented centrally for 0.5 s, and after a delay of 8.5 s, they rotated a needle on an orientation wheel to match that of the remembered orientation as precisely as possible. The orientations in the samples were drawn equally from the orientation space (0-180°) across trials. Behaviorally, the distribution of participants' responses was non-uniform, consistent with previous findings. To investigate how this bias was implemented neurally, for each condition and each time point we trained inverted encoding models (IEMs) using participants' behavioral responses. Plotting the distribution of the peak response orientations revealed that, in both early visual and parietal cortex, the distribution of these neural representations of response bias closely tracked the landscape of the subjects' prior distributions of orientation space, even during the earliest time points of a trial. This brain-behavior correlation was highest in the 0%-contrast trials, where neural activity was uninfluenced by sensory signals. The trial-specific neural representation of the impending

response, in contrast, did not emerge until several seconds into the trial. These results suggest that prior knowledge is a stable attribute that is represented within the neural network, which could help to adjust and stabilize mnemonic representations on a trial-by-trial basis.

Disclosures: Q. Yu: None. **B. Postle:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.14/BB36

Topic: H.02. Human Cognition and Behavior

Support: NIH Grant R01MH087214
ONR Grant N00014-15-1-2790

Title: Neural dynamics of interrupting active working memory

Authors: *N. HAKIM[1], T. FELDMANN-WUSTEFELD[2], E. AWH[3], E. K. VOGEL[1]; [1]Univ. of Chicago, Chicago, IL; [2]Univ. of Southampton, Chicago, IL; [3]Psychology, Univ. of Chicago Dept. of Radiology, Chicago, IL

Abstract: We rely on working memory (WM) to keep information in mind. Recent research that we have conducted has shown that there are two neurally dissociable sub-component processes, item-based storage and spatial attention, that support the maintenance of information in active WM (Hakim, et al., 2019). In this series of experiments, we recorded electroencephalography (EEG) activity while participants performed tasks where we manipulated the demands for item-based storage independently of sustained spatial attention. We found that the Contralateral Delay Activity (CDA), which is a difference in amplitude between contralateral and ipsilateral electrodes, tracked item-based storage. On the other hand, lateralized alpha power (8-12 Hz), which is a difference in power between contralateral and ipsilateral electrodes, tracked spatial attention. Here, we use these two "online" measures of active WM to more finely delineate how task-relevant and task-irrelevant interruption influence item-based storage and spatial attention. In Experiment 1 (n=20), we had participants perform a color change detection task during which task-irrelevant interrupters appeared on a subset (25%) of trials. Following interruption, item-based representations, as indexed by the CDA, sustained for several hundred milliseconds, but were lost by the end of the trial. On the other hand, spatial attention, as indexed by lateralized alpha power, immediately shifted away from the memory locations, but re-oriented back towards these locations by the end of the trial. These results suggest that item-based representations can persist outside the focus of attention. Additionally, spatial attention and item-based storage are distinct, but work together to protect information in active working memory. In Experiment 2 (n=20) and 3 (n=20), we manipulated the relevance of the interrupters. In the task-irrelevant

block, participants had to ignore the interrupters, and in the task-relevant block they had to discriminate the shape of the interrupters. In Experiment 2, we found that memory items, as indexed by the CDA, were dropped more quickly when interrupters were relevant than when they were irrelevant. Additionally, spatial attention, as indexed by lateralized alpha power, more quickly shifted away from the locations of the memory items when interrupters were relevant than when they were irrelevant. In Experiment 3, we extended these findings by showing that relevant interrupters were encoded, but irrelevant interrupters were suppressed. Overall, this series of experiments illustrates that dissociable neural indices of active WM distinctly and dynamically respond to varying task demands.

Disclosures: **N. Hakim:** None. **T. Feldmann-Wustefeld:** None. **E. Awh:** None. **E.K. Vogel:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.15/BB37

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH087214
ONR N00014-15-1-2790

Title: Multivariate decoding of visual working memory load from the human EEG signal

Authors: ***W. S. THYER**[1], K. C. ADAM[2], E. VOGEL[1], E. AWH[1];
[1]Psychology, Univ. of Chicago, Chicago, IL; [2]Psychology, UCSD, La Jolla, CA

Abstract: Neural signals that can track information stored in visual working memory (WM) provide a powerful tool for tracking the contents of this online memory system. Although univariate signals from human EEG such as contralateral delay activity (CDA) (Vogel and Machizawa 2004) and alpha power suppression (Fukuda et al. 2015) have proven to be robust indices of WM storage, differentiating WM load using these univariate signals requires averaging across dozens or even hundreds of trials per condition. We propose that multivariate analysis of EEG voltage topography may provide higher sensitivity, enabling tracking of WM storage loads even at the level of single trials. First, we tested feasibility of decoding methods using published datasets with CDA (Unsworth et al. 2015; n = 183) and alpha power (Fukuda et al. 2015; n = 30). We found robust decoding of memory load, even when training and testing on single trials. However, in both of these experiments, visual stimulation increased linearly with memory load, potentially confounding our ability to classify memory load. In a new experiment (n = 25), we controlled for this confound by manipulating the number of stored items (1-4) while holding visual stimulation constant. To visually match displays, we presented luminance-

matched filler stimuli along with the memoranda (i.e., participants always saw 5 luminance-matched objects, but encoded only a subset into WM). Using logistic regression, we observed robust decoding of the number of targets in the sample display. Cross training analyses suggested that this multivariate load signal evolved dynamically just after sample onset, but achieved a temporally-generalizable pattern during the final 750 ms of a 1000 ms delay period. Thus, scalp topography of EEG voltage contains robust information regarding online storage loads in visual WM in the absence of confounds in stimulus-evoked activity.

Disclosures: W.S. Thyer: None. **E. Awh:** None. **E. Vogel:** None. **K.C. Adam:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

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Program #/Poster #: 517.16/BB38

Topic: H.02. Human Cognition and Behavior

Support: the National Natural Science Foundation of China (grant number 31571115 to H.L.)
Beijing Municipal Science & Technology Commission (Grants Z181100001518002)

Title: Distinct encoding characteristics in occipital and parietal areas during human sequence memory

Authors: *Q. HUANG, H. LUO;
Sch. of Psychological and Cognitive Sciences, Peking Univ., Beijing, China

Abstract: Temporarily maintaining a sequences of items is important in many cognitive functions, yet the underlying dynamic neural mechanisms and the functions of different brain regions in the process remain unclear. In the present study, we recorded magnetoencephalography (MEG) signals from 24 subjects when they held a two-orientation sequence in working memory. We employed a time-resolved multivariate decoding approach to assess the representation tuning curves for the two sequentially memorized orientations respectively. First, significant recency effect were found in memory behavior (i.e., $2^{nd} > 1^{st}$). Interestingly, during the memory maintaining period, occipital and parietal areas showed distinct encoding characteristics for the two-orientation sequence. Specifically, occipital cortex seemed to employ a type of "power encoding" approach, such that the 2^{nd} item showed stronger decoding strength than the 1^{st} item, whereas their decoding latencies were not different. In contrast, the parietal area displayed a "temporal encoding" profile, during which the 2^{nd} item had earlier latency in the decoding time course compared to the 1^{st} item, whereas their overall decoding strength were similar. Finally, the power- and time-based encoding in the occipital and parietal

areas continued in the recalling period and was strongly associated with recency effect in behavioral performance. Taken together, our results demonstrate distinct and dissociated encoding characteristics of occipital and parietal areas in sequence memory, through which a list of items as well as their relationship would be rapidly represented and organized in working memory.

Disclosures: Q. Huang: None. **H. Luo:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.17/BB39

Topic: H.02. Human Cognition and Behavior

Support: MRC IMPACT DTP studentship awarded to O. Ratcliffe

Title: The temporal dynamics of working memory maintenance in a category-based N-Back

Authors: *O. J. RATCLIFFE, B. STARESINA, K. SHAPIRO;
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Abstract: A popular theoretical framework suggests that theta-gamma coupling facilitate the short-term retention of several serial items in working memory (WM). According to this model, temporal order is maintained through theta phase coordination and individual items are represented by gamma bursts occurring sequentially during the upstate of the ongoing theta wave. Several lines of evidence point to these two frequency bands being involved: e.g. frontal gamma increases with item load and theta:gamma ratios predict individual WM capacity. However this evidence does not directly show specific content being maintained in slots, as the model would predict. In this study we used multivariate pattern analyses (MVPA) to track reactivation of category-specific working memory representations over the course of an N-Back task.
33 subjects (aged 18-35) participated in two tasks. The first task was a delayed-match-to-sample (DMS) task using three categories of stimuli: faces, objects, and scenes. This task was completed twice, before and after the N-Back. Stimulus timings remained the same in the N-Back as in the DMS. The N-Back task consisted of 12 blocks: 8 2-back, 4 1-back. The N-Back task used two of the previous categories, objects and scenes, so that faces could serve as a neutral stimulus category for subsequent multivariate analyses.
Behavioural accuracy was high in all three tasks: 94% on the DMS, 93% on 1-back trials, and 92% on 2-back trials. Time-frequency analyses demonstrated increases in frontal theta power during the delay period that scaled with working memory load. Conversely, fronto-central beta

power decreased in the delay period of 2-back trials as compared to the 1-back. Classifiers were then trained on EEG data and cross-validated in a leave-one-out procedure. Overall, classification was highest when the stimulus was on screen. Accuracy then reduced before a second peak was observed during the response portion of the task, suggesting neural reactivation of the WM representation. Decoding during the delay period appeared to show some rhythmic reactivation. Frequency transformation of the classifier decision values of individual trials was performed to examine whether category reinstatement oscillated in any of the canonical frequency bands.

Disclosures: O.J. Ratcliffe: None. **B. Staresina:** None. **K. Shapiro:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.18/BB40

Topic: H.02. Human Cognition and Behavior

Support: PhD scholarship German Academic Scholarship Foundation (awarded to C.F.)

Title: Congruent context features enhance integration and attenuate separation of working memory representations across and within memory episodes

Authors: *C. FISCHER[1], S. CZOSCHKE[1], B. PETERS[1], B. RAHM[2], J. KAISER[1], C. BLEDOWSKI[1];
[1]Inst. of Med. Psychology, Goethe Univ., Frankfurt am Main, Germany; [2]Med. Psychology and Med. Sociology, Albert-Ludwigs-University Freiburg, Freiburg, Germany

Abstract: Working memory (WM) provides a direct access to a limited number of object representations that are often conceptualized as bundles of integrated content and context features. Those object representations need to be maintained in a stable but distinguishable manner over time, which requires integrating corresponding inputs as well as reducing interference between concurrently maintained objects by separation. In line with this notion, recent studies showed that WM representations are not maintained independently, but interact across and within memory episodes, in particular when their task-relevant contents are similar to each other. Those interactions can be repulsive or attractive, pointing towards a separating or integrative mechanism, respectively. We hypothesized that integration should be enhanced whereas separation should be attenuated in situations where two representations are likely to represent the same object, i.e. share similar context in addition to their content features. We asked participants to remember the motion directions (content feature) of two sequentially presented colored dot fields (S1 and S2) per trial. One item per trial was retro-cued for continuous report via a context feature, i.e. either by its color (Experiment 1) or serial position

(Experiment 2). We manipulated the congruence of context features of S1 and S2 within and between trials to examine their interactions with content representations. In line with previous findings we observed an attractive bias (i.e. serial dependence across trials) between current and past motion directions, in particular when their content was similar. Moreover, serial dependence across trials was also enhanced when items shared the same color or serial position across trials. In contrast, within a trial we observed a repulsive bias from S1 on S2 (i.e. within-trial serial dependence) that was attenuated by congruent context features. Taken together, our results confirmed our hypothesis that congruent context features promote integration by enhancing attraction between WM representations with similar contents across trials and by attenuating their repulsion within a trial. These findings suggest a context-dependent interplay of integration and separation in WM that helps to balance demands for stable object identity and object distinctiveness across or within a memory episode. Future experiments will aim at the identification of the neural mechanisms subserving integration and separation and their interaction with context congruency.

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Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.19/BB41

Topic: H.02. Human Cognition and Behavior

Support: National Multiple Sclerosis Society Pilot Research Grant
Mark Diamond Grant from the University at Buffalo

Title: Neurophysiological indices of the transfer of cognitive training gains to untrained tasks in multiple sclerosis patients

Authors: *T. J. COVEY, Z. TURTOLA, J. L. SHUCARD, X. WANG, D. W. SHUCARD; Neurol., Jacobs Sch. of Med. and Biomed. Sciences, Univ. at Buffalo, Buffalo, NY

Abstract: Multiple Sclerosis (MS) is a neurodegenerative disorder that can negatively affect cognition and day-to-day functions. Cognitive rehabilitation interventions may improve these functions in MS, but the research in this area has yielded mixed findings. The efficacy of cognitive rehabilitation may vary according to the specific cognitive domains that are targeted by a given protocol, and also based on individual differences in disease progression that can impact cognition and neural plasticity. Here we present preliminary analyses that sought to reveal the extent that a targeted cognitive training protocol could improve performance outcomes and change brain function for untrained cognitive tasks in MS patients. MS (n = 12) and healthy

control participants (n = 12) completed twenty sessions of adaptive working memory (WM) training (n-back task, visually presented letter stimuli), over 4-5 weeks. A WM training protocol was selected because it has been well-studied in healthy individuals, and WM and related processes (i.e., processing speed, executive functions) are commonly impaired in MS. All study participants completed a battery of cognitive tests at baseline (pretest) and after completing the training protocol (posttest). Event-related potential (ERP) indices of brain activity were derived from participants' ongoing EEG activity that was collected at pretest and posttest for untrained tests of spatial WM (spatial 3-back), cognitive control (Go/NoGo flanker task), and selective attention (visual search task). Both MS and control groups demonstrated significant improvements in a broad range of cognitive outcome measures. Furthermore, enhancements in ERP indices of target detection, attention, and executive control were observed for both groups after training. MS patients and controls both had pretest-to-posttest enhancement of N1 amplitude for the spatial WM task, and enhancement of P2 and N2 amplitude for the cognitive control and selective attention tasks. In contrast, the control group exhibited more pronounced pretest-to-posttest enhancement of P3 amplitude, overall, than the MS group. These analyses identified neural activity associated with the transfer of WM training gains in MS. These training-induced neural changes corresponded with pretest-to-posttest improvements in cognitive performance. The findings also indicate that some neural processes (i.e., P3) may be less responsive to cognitive training in MS, possibly due to the occurrence of disease processes.

Disclosures: **T.J. Covey:** 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.; Co-PI NMSS Research Grant, Co-PI NIJ Research Grant. F. Consulting Fees (e.g., advisory boards); Biogen Consulting Fee. **Z. Turtola:** None. **J.L. Shucard:** None. **X. Wang:** None. **D.W. Shucard:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.20/BB42

Topic: H.02. Human Cognition and Behavior

Support: NIH R01MH087214
ONR N00014-15-1-2790

Title: Sustained slow wave activity and alpha oscillations index distinct aspects of storage in working memory

Authors: *G. K. DIAZ, E. K. VOGEL, E. AWH;
Dept. of Psychology, Univ. of Chicago, Chicago, IL

Abstract: Multiple neural signatures have been implicated in the maintenance of information in visual working memory (WM). Using EEG recorded from parieto-occipital electrodes on human subjects, we replicated past observations that increasing WM load leads to monotonic increases in the amplitude of a sustained negative slow wave and monotonic declines in oscillatory brain activity in the alpha-band (8-12 Hz). Although both of these EEG signals track WM storage load, they appear to play separable functional roles. For example, previous research has found that these two signals have distinct time courses and explain unique variance in WM capacity across individuals (Fukuda et al., 2015). Our working hypothesis is that the negative slow wave is an item-based signal that tracks the number of individuated representations in WM, while alpha power indexes the locations of the stored items. In a prior study, we manipulated the number of perceived items using perceptual grouping, while holding constant the number of locations occupied by memoranda. We found that the negative slow wave, but not alpha power, tracked the number of perceived items. Here, we extended this work by using sequentially presented displays to manipulate the total number of locations occupied by a given number of memoranda. Alpha power, but not slow wave activity, tracked variations in the total number of locations when the number of items stored was held constant. By contrast, slow wave activity tracked the total number of items stored, but did not vary with the number of locations occupied by the memoranda. Overall, the current work provides additional evidence that alpha power and the negative slow wave from parieto-occipital electrodes track distinct aspects of WM storage, such that slow wave activity indexes the number of items stored, while alpha activity indexes the number of prioritized locations.

Disclosures: G.K. Diaz: None. **E.K. Vogel:** None. **E. Awh:** None.

Poster

517. Human Working Memory: Mechanisms I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 517.21/DP12/BB43

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster

Topic: H.02. Human Cognition and Behavior

Support: K23-NS104252

Title: Spatiotemporal dynamics of associative memory processing in patients with focal epilepsy

Authors: S. HENIN[1], A. SHANKAR[4], H. BORGES[1], D. FRIEDMAN[1], A. FLINKER[1], W. DOYLE[2], O. DEVINSKY[1], G. BUZSAKI[3], ***A. A. LIU**[1];
[1]Neurol., [2]Neurosurg., [3]Neurosci. Inst., New York Univ. Sch. of Med., New York, NY; [4]The Ohio State Univ., Columbus, OH

Abstract: BACKGROUND. Memory dysfunction impacts 40-50% patients with epilepsy, affecting work, school, and everyday life. Interictal spikes during verbal encoding have been associated with forgetting but their relationship to memory physiology is unclear. Epilepsy patients undergoing invasive electroencephalography (iEEG) for resective surgery provide an opportunity to dissect the fine-grained spatiotemporal dynamics of memory. OBJECTIVE. We describe the time course of high gamma activity (HGA), a measure of local population firing, across the brain during associative encoding. Next, we examined the impact of spikes on memory encoding in regional and network level analyses. METHODS. A computerized associative memory task was used to probe memory function in surgical epilepsy patients at NYU Langone Health. Electrode localization was performed using automated processes and expert review to identify spikes. Analysis focused on determining differences in the spectral-temporal features in the high-gamma activity (HGA) between successful and failed encoding as well as investigating the impact of spikes on successful encoding. RESULTS. Eight patients undergoing invasive EEG were included. Both successful and failed encoding trials demonstrated an early peak (<0.5 s) and sustained (0.5-2s) HGA in primary visual (occipital), visual association (inferior parietal), and high-level visual recognition (fusiform) cortex. Successful trials demonstrated greater HGA during late (1-2 s) encoding in bilateral medial temporal memory regions (entorhinal cortex, hippocampus, and amygdala) compared to failed trials. Late (1-2 s) differences in HGA in frontal executive and sensorimotor (primary motor, supplementary motor, pars triangularis/orbitalis, superior temporal gyrus) were associated with encoding performance. Right hemisphere demonstrated a different time course of HGA compared to left hemisphere, with greater differences in HGA distinguishing successful versus failed trials. Spikes occurring in bilateral medial temporal (L and R hippocampus, L entorhinal) during encoding were associated with a 2.0 greater odds of forgetting. CONCLUSIONS. In a cross-modal associative memory task, sustained neural activity in memory, executive/attentional, and sensorimotor networks characterized successful encoding. Differences in left and right hemisphere activity likely reflect specialization of word and face processing. Spikes in bilateral medial temporal lobe disrupt encoding.

Disclosures: S. Henin: None. **A. Shankar:** None. **H. Borges:** None. **D. Friedman:** None. **A. Flinker:** None. **W. Doyle:** None. **O. Devinsky:** None. **G. Buzsaki:** None. **A.A. Liu:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: H.02. Human Cognition and Behavior

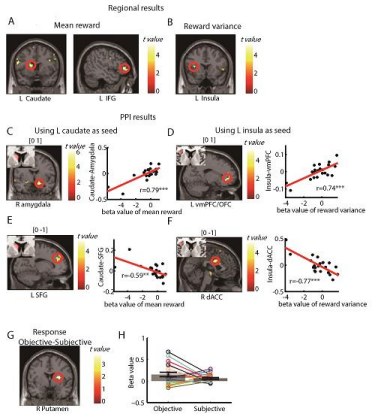
Support: Singapore Ministry of Education (MOE) Tier 1 grant (FY2015-FRC2-018)
MOE Tier 2 Grant (MOE2014-T2-2-016)

Chinese Postdoctoral International Exchange Program

Title: Distinct neural correlates underlie mean reward and reward variance in risky decision making: Evidence from eye-tracking and fMRI

Authors: *S. SUN[1], R. YU[2];
[1]Caltech, Pasadena, CA; [2]Psychology, Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Value-based decisions are influenced by both expected utility and potential risks of outcomes. However, most previous studies failed to separate the expected value from risks. Using a new incentivized reaction time (RT) task in which mean reward (expected utility) and reward variance (potential risks) of two values were parametrically manipulated and orthogonalized, we examined the neural correlates of expected utility and risk, and how these representations lead to subjective decisions. We show that RTs (n = 90) varied as a function of mean reward, suggesting that expected utility is the main driver of reward motivation. Moreover, gaze transitions (n = 68) tracked mean reward, indicating that participants shifted gaze more towards higher expected utility. Pupil size tracked the variability of RTs, possibly reflecting the emotional arousal induced by subjective risk preference. Neuronally (n = 22), the striatum tracked mean reward, and its connectivity with amygdala and SFG were correlated with expected utility. The insula tracked reward variance, and its connectivity with vmPFC and dACC was associated with potential risks. Computational modeling further shows that the putamen conveyed subjective utility by integrating both expected value and risks. We provide the first evidence that expected utility and risks were encoded differently at behavioral, attentional, and neural levels. These results extend existing evidence by showing that expected utility engages the striatal-cortical limbic motivational network in pursuing high reward, whereas risk associates with cingulo-insular salience network in detecting reward conflicts, together initiate subjective utility as conveyed by the pupil-linked arousal system and striatum. The results are discussed in terms of theory and application.
Key words: mean reward, reward variance, expected utility, risk, motivation, fMRI



Disclosures: **S. Sun:** None. **R. Yu:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.02/BB45

Topic: H.02. Human Cognition and Behavior

Support: NSF DG31746891

Title: Competing decision making strategies in a fixed odds game: The subversive role of the reinforcement learning network

Authors: *C. R. STEINHARDT[1], S. V. SARMA[2];
[2]Biomed. Engin., [1]Johns Hopkins Univ., Baltimore, MD

Abstract: The underlying neural circuitry that a person uses to make decisions on a daily basis has evolved from millennia of evolutionary pressure on animals to make decisions about food, danger, and mate choice for the purpose of survival. The human brain performs reinforcement learning (RL), accumulation of evidence with repeated exposure to a stimulus that leads to an estimate of the amount and likelihood of reward gained from an object, as other animals do. Additionally, humans have developed other cognitive functions, including the ability to learn and make decisions based on instructions, rule-based learning (RBL). These strategies are both actively used for decisions on a personal level, such as choices of self-presentation or lifestyle (e.g. dietary choices), and, on larger scales, such as management of funds for a company. The adaptability of human cognition can be a disadvantage, as people can acquire biases towards dangerous behaviors, such as gambling, and show tendencies towards choices against known fixed odds. We hypothesize that these counter-factual decisions may be a result of RL overriding RBL in such situations. To test our hypothesis, we performed a study designed to elicit changes in decision strategy. Ten human subjects (3 M, 36.2 +- 3.8 years old) performed a sequential decision task in which on each trial a card was drawn from an infinite deck with fair probabilities, and they needed to bet $5 (low) or $10 (high) on the probability of the first card they are shown being higher than the next (which can be higher, lower, or the same). At the same time, EEG recordings were acquired from depth electrodes implanted for clinical purposes. Although the task had fixed probabilities, subjects show changes in betting behavior over time for the same card values. Additionally, some betting defies the optimal betting strategy (i.e., maximizing expected reward), such as betting high on a card with less than 50% chance of winning. To capture variability in each subject's betting behavior, we built subject-specific logistic regression models that predicted the probability of betting high as a function of RBL and RL variables. These models demonstrate which strategies (RBL vs RL) may be influencing changing beliefs and in turn gambles over trials. We concluded that certain subjects are consistently using RBL, while others are switching between betting using RBL and allowing RL

to outweigh the RBL choice. We then identified RL and RBL neural networks by examining power spectra of neural activity across the population, and found that the level activation of these networks explained variability in decision making observed.

Disclosures: C.R. Steinhardt: None. **S.V. Sarma:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

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Program #/Poster #: 518.03/BB46

Topic: H.02. Human Cognition and Behavior

Support: NRF-2018R1D1A1B0704358 to DC
UNIST-1.190092.01 to DC
NRF-2018R1A2B6008959 to OSK

Title: Humans over-expect from the future chances in finite sequential decision problems

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Abstract: Many decision problems in life are sequential and constrained by a certain time window. 'Secretary problem' is a classic example of this finite sequential decision problem; one has to make a choice whether to accept the current applicant, a rejected applicant does not get a second chance, and there are usually no chances to review other potential applicants when the position is filled. Although the problem can be mathematically solved, it is not clear whether and how humans deviate from the optimal behaviors. Here, we used one variant of a secretary problem to investigate (i) whether individuals make an optimal decision in a finite sequential decision problem, and (ii) if not, how their decisions are made. During the task, participants were asked to accept or reject after viewing a random number. On each round, they could have up to five chances to evaluate a new random number by selecting reject. When they accepted, the presented number was accumulated to their final payoff, and then they moved on to the next round (up to 200 rounds) that consisted of a new set of five chances. We computed a decision criterion for acceptance at each chance that best explained participants' choices. Participants showed higher threshold compared to optimal decision criteria indicating that they were expecting a higher payoff from the future chances than they could actually earn. This behavioral tendency was successfully explained by an optimal decision model with individuals' utility function parameterized by reference point and value sensitivity. We confirmed that difference between the presented values and the model estimated thresholds explains the speed of participants' responses at each chance. Furthermore, participants' physiological responses,

measured by their pupil dilation at keypress reflected the same pattern (a function of difference between value and the threshold rather than values *per se*). These results support our proposed model suggesting that individuals make threshold-based choices in a finite sequential decision problem, and seemingly suboptimal decision patterns (waiting for future chances) may be originated from the process of calculating thresholds using individuals' utility function.

Disclosures: Y. Shin: None. **H. Seon:** None. **Y. Shin:** None. **D. Chung:** None. **O. Kwon:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.04/BB47

Topic: H.02. Human Cognition and Behavior

Support: NIDA Grant 5R01DA040990-04

Title: Menu complexity effects on attribute integration in risky multi-attribute decision making

Authors: *J. G. ELSEY[1], Y.-P. YANG[1], E. EMERIC[2], E. NIEBUR[3], V. STUPHORN[3]; [1]Psychological and Brain Sci., [2]The Zanvyl Krieger Mind/Brain Inst., [3]Dept. of Neurosci., Johns Hopkins Univ., Baltimore, MD

Abstract: When evaluating multiple risky alternatives, the values of each alternative's attributes are integrated such that preference dynamically evolves to form one's ultimate choice. Past studies have presented subjects with choice menus that are limited in alternative and attribute complexity, or where attributes were not parametrized. We therefore presented subjects with choice scenarios more complex than simple two-alternative risky choice menus, and more explicitly-defined than previous large choice menus. In this study, we investigate attribute integration strategies underlying preference formation in increasingly complex risky choice menus.

We tested subjects in variations of a decision making tasks that differed in the number of alternatives and attributes presented. In the first experiment, subjects were offered two or three alternatives with two attributes: reward amount and probability of earning reward. In the second experiment, subjects were presented with four alternatives that consisted of four attributes: reward amount, loss amount, probability of earning reward, and wait time for outcome feedback. Attribute stimuli are displayed in spatially separate locations within a boundary cue indicating that they belong to the same alternative. Each attribute's magnitude is masked by its corresponding color cue, which is only revealed when fixated upon. Subjects are allowed to freely inspect the attributes with no time constraint, before choosing. The eye movements provide temporal and spatial information about subjects' focus of attention during attribute

integration.
Subjects exhibited two different attribute integration strategies: (1) a within-alternative strategy (i.e. inspecting the attributes within one alternative, then inspecting the attributes within another alternative), and (2) a within-attribute strategy (i.e. inspecting the same attribute type across alternatives, then inspecting a different attribute type across alternatives). At the population level, subjects favored a within-alternative strategy in both the 2-alternative, 2-attribute (within-alternative: 44%, within-attribute: 29%) and 3-alternative, 2-attribute choice menus (within-alternative: 42%, within-attribute: 33%). However, past studies have shown that subjects faced with many more alternatives consisting of a greater number of attributes they predominantly use a within-attribute strategy. This aim of this study will to be to systematically investigate when the shift in integration strategy occurs as menu complexity increases.

Disclosures: J.G. Elsey: None. **Y. Yang:** None. **E. Emeric:** None. **E. Niebur:** None. **V. Stuphorn:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.05/BB48

Topic: H.02. Human Cognition and Behavior

Title: A computational model for cognitive fatigue in individuals with multiple sclerosis

Authors: *F. R. ERANI[1], J. D. MEDAGLIA[2];
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Abstract: Fatigue is experienced in up to 90% of individuals with multiple sclerosis (MS) and is a primary cause of disability in MS. Despite extensive research, the basic mechanisms that cause fatigue in MS are poorly understood, and as such, have slowed progress on interventions that target fatigue. The cognitive component of fatigue is generally the most distressing aspect of patients' fatigue because it limits their ability to sustain concentration and endure mental tasks. Reward and cognitive control research, along with corroborating neuroimaging findings, provide evidence that suggest the processes behind this symptom. This literature suggests that there is a reward/cognitive effort imbalance or a disruption in one or both of these functions in individuals with MS who experience cognitive fatigue. However, how the specific mechanisms of reward, cognitive control, and the anticipated rewards for exerting effort have not been clarified. To better characterize the processes behind cognitive fatigue, we introduce a model that builds upon the existing theories and include Shenhav and colleagues' (2013) expected value of control (EVC) theory. We use the model to demonstrate specific simulated cases in which fatigue would occur in individuals with 1) deficits in cognitive control, 2) deficits in reward processing, and 3) deficits in the ability to estimate the EVC. Our results indicate that model [1] less baseline

cognitive control or having less cognitive control to deploy due to MS pathology and model [2] baseline reward blunting or blunting due to MS pathology, result in early and fast increases in cognitive fatigue. Model [3] reveals that an inability to calculate the expected value of reward results in disengagement from the task altogether, preventing the ability to measure cognitive fatigue by avoiding it altogether. Moreover, dysfunctional cognitive control and reward processing, and subtle abnormalities in EVC interact to produce greater cognitive fatigue than each separately. Taken together, our results suggest that cognitive fatigue can result from one or more neurocognitive sources, and that similar levels of fatigue can imply differences in how interventions should be targeted in MS and potentially other neuropsychological syndromes.

Disclosures: F.R. Erani: None. **J.D. Medaglia:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.06/BB49

Topic: H.02. Human Cognition and Behavior

Title: Modulation of 1/f noise emitted in reaction time: Independent effects of increasing uncertainty of "when" and "what" in stimulus presentation

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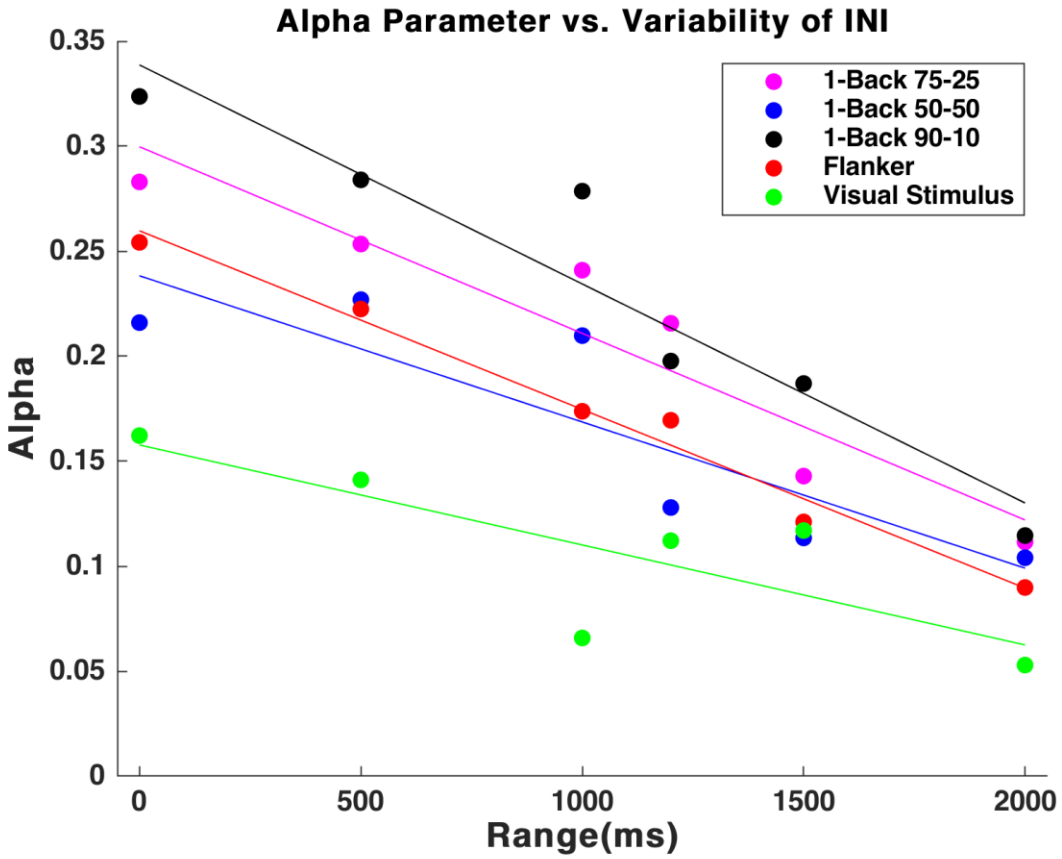
Abstract: Measurement of Reaction Time (RT) in speeded decision processing tasks has shown a large intra-subject variability of RT (ISV-RT). Decomposing the frequency spectrum of the underlying time series of the RT have shown that ISV-RT may be rooted at a long memory process called 1/f noise. 1/f noise is theorized to be a characteristic signature for system complexity and has been associated with the most elementary aspect of cognitive process, the formation of representations. In this study we investigate how the emergence of 1/f noise is affected by different conditions of "stimulus time" and "stimulus type" predictability. 15 healthy volunteers performed the 1-Back working memory task, the Eriksen flanker spatial attention task and a two-choice simple visuomotor task. Six different task conditions were used for every task in which the inter-trial interval (ITI) was either fixed at 1s, or varied in a uniform distribution of ITI with a mean of 1s and range of.5, 1, 1.2, 1.5, 2s respectively. For the 1-Back task, the power spectrum was also investigated in three conditions of "stimulus type" predictability; more specifically the proportion of the two alternative responces was 50:50, 75:25 and 90:10 in different blocks. The spectrum density of RT confirmed the presence of 1/f noise measured as a

decreasing linear trend a in the log-log scale indicating higher power at low frequencies that was reduced in higher frequencies. More importantly this 1/f noise (alpha parameter)decreased significantly with increasing uncertainty regarding either the stimulus timing or the stimulus response-type, indicating two independent sources of 1/f noise (see figure1). These results suggest that the cognitive process of formation of stable representations revealed in the presence of 1/f noise in RT is sensitive to predictability of when and what in stimulus presentation.



Disclosures: **P. Alefantis:** None. **C. Siettos:** None. **I. Alefanti:** None. **N. Smyrnis:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.07/BB50

Topic: H.02. Human Cognition and Behavior

Support: JSPS KAKENHI Grant Number JP26242087

JSPS KAKENHI Grant Number JP17H06314
JST CREST Grant Number JPMJCR15E4

Title: Identifying intuitive and reflective social decision processes

Authors: *S. NUMANO[1,2], T. NIHONSUGI[3,2], M. HARUNO[2,1];
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Abstract: Our decision process has been postulated to comprise dual processes: intuitive (fast) and reflective (slow) ones (Sloman, 1996). The dual process theory is particularly important in social interactions (Evans, 2008) in which multiple neural processes need to be integrated. However, neural mechanisms underlying dual social decision processes remain poorly understood partly due to methodological limitations to model dual social processes. Here, we introduced a parametric drift-diffusion for social interactions, and used it to analyze behavioral and functional magnetic resonance imaging (fMRI) data of a trust game (Nihonsugi *et al*., 2015). In our online behavioral experiment (N=4043), we constructed parametric drift-diffusion which can include constant, self-reward, other-reward, inequity and guilt in its bias and drift terms and selected the best model based on predictive likelihood of unseen data which was not used for model estimation. In the fMRI experiment of the same trust game (N=45), we analyzed participants' behavior based on the best model selected in the online experiment. The best model includes a constant and inequity in the bias term, and a constant, self-reward, inequity, and guilt in the drift term, indicating that inequity comprises dual processes. Therefore, we conducted a clustering of participants based on the model's coefficients for bias inequity and drift inequity and identified two groups: "bias group" and "drift group". Next, we contrasted fMRI data correlated with inequity between the two groups (using SPM12). We found that the "bias" group exhibited activity in the ventral striatum and insula, and the "drift" group on the other hand, showed activity in the caudate nucleus, anterior cingulate, and dorsolateral prefrontal cortices (*P* < 0.001; uncorrected for multiple comparison). This result suggests that these two groups of brain structures play a critical role in intuitive and reflective inequity aversions, respectively.

Disclosures: S. Numano: None. **T. Nihonsugi:** None. **M. Haruno:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.08/BB51

Topic: H.02. Human Cognition and Behavior

Title: Experience and stress management training strategies ameliorate phasic and tonic electrodermal activities independently during critical simulated situations

Authors: *D. CLAVERIE[1], F. SIGWALT[2], J.-N. EVAIN[4], M. BUI[5], A. GUINET-LEBRETON[6], M. TROUSSELARD[7,9], F. CANINI[8,10], D. CHASSARD[2,11], A. DUCLOS[3,12], J.-J. LEHOT[2,11,12], T. RIMMELÉ[2,11,13], M. LILOT[2,11,12];
[1]IRBA, BRETIGNY SUR ORGE, France; [2]Dept. d'anesthésie-réanimation, [3]Pôle Information Médicale Evaluation Recherche, Hospices Civils de Lyon, Lyon, France; [4]Dept. of Anaesthesia and Intensive Care, Grenoble Alpes Univ. Hosp., Grenoble, France; [5]Hop. d'Instruction des Armées Desgenettes, Lyon, France; [6]Ctr. Médical des Armées, Service de Santé des Armées, Varces Allières et Risset, France; [7]Inst. of Biomed. Research, Armies' Hlth. Service, Bretigny-sur-Orge, France; [8]Inst. of Biomed. Research, Armies' Hlth. Service, Brétigny-sur-Orge, France; [9]Ecole du Val de Grâce, 1 place A. Laveran, Paris, France, France; [10]Ecole du Val de Grâce, 1 place A. Laveran, Paris, France; [11]Univ. Claude Bernard Lyon 1, Ctr. Lyonnais d'Enseignement par Simulation en Santé, SAMSEI, Lyon, France; [12]Hlth. Services and Performance Res. Lab. (EA 7425 HESPER), Univ. Claude Bernard Lyon 1, Lyon, France; [13]EA 7426 – "Pathophysiology of Injury Induced Immunosuppression", bioMérieux, Lyon, France

Abstract: Critical resuscitation situations are very stressful for caregivers. Acute stress is known to decrease performance. Stress management training might help participants to improve performance and their stress management strategies. High-fidelity simulation (HFS) can help test this hypothesis, since HFS is known to induce acute stress in the participant through immersive and realistic situations. The objective was to test whether Tactics to Optimize the Potential (TOP), as a cognitive stress management program, could improve residents' performance during HFS and could have beneficial effects on the stress reaction. Each resident convened to formative HFS were randomized in two parallel-arms (TOP or control) and actively participated in one HFS scenario. Only residents from the TOP group had specific TOP training few weeks before the HFS and a four-minute TOP reactivation occurring just before the beginning of the scenario. 128 residents were included in the analysis. The overall performance was nine percent higher in the TOP group *vs.* the control group. Phasic EDA did not increase in the TOP group whereas it increased in the control group between the previous period of reactivation and the scenario period. Tonic EDA decreased during the scenario period with years of experience (resident skill) but was not influenced by TOP training. Thus, the TOP group was characterized by a decrease of phasic electrodermal activity, a marker of sympathetic system. This effect was different of effects induced by experience which only modified tonic electrodermal activity. It was at our knowledge the first time that two different processes were shown to influence independently one of the two components of the EDA. Benefits of TOP training should be considered in real clinical emergency settings.

Disclosures: D. Claverie: None. **F. Sigwalt:** None. **J. Evain:** None. **M. Bui:** None. **A. Guinet-Lebreton:** None. **M. Trousselard:** None. **F. Canini:** None. **D. Chassard:** None. **A. Duclos:** None. **J. Lehot:** None. **T. Rimmelé:** None. **M. Lilot:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.09/BB52

Topic: H.02. Human Cognition and Behavior

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COST Action Open Multiscale Systems Medicine (OpenMultiMed) supported by COST (European Cooperation in Science and Technology) (K.W.-L)

Title: Changes-of-mind due to high decision uncertainty: An experimental and computational modelling study

Authors: *N. A. A. ATIYA[1], A. ZGONNIKOV[2], D. O'HORA[3], K. WONG-LIN[1];
[1]Sch. of Computing, Engin. and Intelligent Systems, Ulster Univ., Derry~Londonderry, United Kingdom; [2]Sch. of Computer Sci. and Engin., Univ. of Aizu, Aizu-Wakamatsu, Japan; [3]Sch. of Psychology, Natl. Univ. of Ireland Galway, Galway, Ireland

Abstract: Change-of-mind behaviour is considered a hallmark of cognitive flexibility. Previous perceptual decision-making studies have predominantly proposed that changes-of-mind are associated with fluctuations in noisy sensory information after the initial choice. These studies were supported by the extended drift-diffusion model (DDM) in which stimulus integration continues after the initial decision, taking into account delays in signal transduction and motor preparation (~400ms). In this work we challenge this concept by hypothesising that fluctuation in sensory evidence may not be the sole factor that contributes to changes-of-mind. In our experiment, four human participants observed a random dot kinematogram stimulus for a limited duration (800ms). In the vast majority of change-of-mind trials, hand responses were initiated only after the entire viewing duration. Furthermore, in such trials, after the initial response, the change in direction occurred later than 450ms. Importantly, such changes-of-mind, leaked into motor space, were associated with long initiation (i.e. response) times. Hence, these distinct 'signatures' strongly suggest a mechanism underlying change-of-mind behaviour that is different from sensory fluctuations after the initial choice. Such a mechanism cannot be readily accounted for by existing cognitive models, e.g. extensions of the DDM. To explain this mechanism, we

developed a biologically-motivated neuronal circuit model of decision making, in which decision uncertainty is continuously monitored through an uncertainty-monitoring cortical neuronal population. Our model without post-decision sensory evidence accumulation can account for the observed long initial response times in change-of-mind trials. Furthermore, the model revealed that long response times in change-of-mind trials are closely linked to high decision uncertainty (low decision confidence) levels. More specifically, during change-of-mind trials, high decision uncertainty leads to the appearance of a transient, choice-neutral, stable steady state that prolongs the initial decision. Such a mechanism is consistent with recent neurophysiological evidence of elevated neural activity in the frontal cortex being associated with changes-of-mind and error-correction behaviour. Taken together, our work provides a neuronal circuit computational framework that explains changes-of-mind in the absence of new post-decision evidence.

Disclosures: N.A.A. Atiya: None. **A. Zgonnikov:** None. **D. O'Hora:** None. **K. Wong-Lin:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.10/BB53

Topic: H.02. Human Cognition and Behavior

Title: Behavioral and EEG evidence of negative conformity bias in a value based task

Authors: *H. WU[1], Q. LIU[3], X. XU[4], X. LIU[2];
[1]Inst. of Psychology Chinese Acad. of Sci., Bejing, China; [2]Inst. of Psychology Chinese Acad. of Sci., Beijing, China; [3]Caltech, Pasadena, CA; [4]Sch. of Automation, Wuhan Univ. of Technol., Wuhan, China

Abstract: Objective and rationale
Few study examined the conformity bias (e.g., people showing more susceptibility to negative or positive social influence, and exhibit more conformity on positive or negative evaluations). In this study, we aim to examine whether negative conformity exists and how this effect manifests in both behavioral and neural responses.
Method
Participants: 28 subjects were had normal or corrected-to-normal vision, no neurological history, and no color blinded was reported.
Task: The same as experiment 1 with 160 faces and trials in first round rating and second round rating.
EEG recoding and analysis: EEG data were recorded by a 64-channel NeuroScan system, sampled at 500 Hz/channel, with impedances lower than 5 kΩ. Traditional ERP analysis and time frequency analysis.

Results
We first confirmed a behavioral phenomenon that people showed a negative conformity bias in a value-based judgment task (present peer's ratings after their initial ratings to faces). Combined with reinforcement learning computational modeling in the first round ratings, we found the comparison of the two learning rate parameters representing positive and negative influence on norm updating showed that participants with higher update score for negative social influence than positive influence. The t-test between negative conformity score and positive conformity score indicated a significant difference, indicating a significant higher conformity score for peers-lower condition than peers-higher condition. The behavioral results indicate a bias to update ratings after more negative ratings from others in the first round ratings, and then people are more likely to adjust their rating towards negative direction in second round rating for peer-lower condition.
We also found EEG signatures (i.e., conflict-related N400 component and theta band EEG) of conformity is stronger for negative social influence direction compared with positive social influence direction. A further correlation confirmed that only theta band power for negative social influence can predict the whole social conformity to majority opinion.
Conclusions
The present investigation provide further perspective on how broadly valid it is that negative information is stronger than good. The present work also provided the temporal profile of social conflict processing as revealed by ERP (e.g., N400) and oscillation (theta band activity) patterns, which identified consistent evidence of stronger neural response to the peers-lower condition.

Disclosures: H. Wu: None. **Q. Liu:** None. **X. Xu:** None. **X. Liu:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.11/BB54

Topic: H.02. Human Cognition and Behavior

Title: Accumulation of evidence during decision making in obsessive-compulsive disorder patients

Authors: *Y. CHEN[1], Y. LIU[2], Q. FAN[2], T. YANG[1];
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Abstract: Decision making often entails the accumulation of evidence. Prior studies have suggested that the obsessive-compulsive disorder (OCD) patients' decision making differs from healthy controls. Both their compulsive behaviour and compulsive thoughts may influence the evidence accumulation process, yet the experimental investigations have been lacking. In the current study, a probabilistic categorization task paradigm has been employed to investigate the

evidence accumulation process during decision making in OCD patients. In the task, subjects made decisions by viewing a sequential presentation of visual stimuli, which were arrows of two directions at 5 different contrasts. In each trial, the stimulus sequence was generated by sampling with replacement from a pool of ten arrow stimuli, whose distribution depended on the correct answer. The subjects were asked to judge whether the overall contrast of the left arrows or the right arrows were higher and report their choices by pressing either the left or the right arrow key on a keyboard. Thus, each presentation of arrow stimulus furnished a piece of probabilistic evidence toward the corresponding choice with the contrast represented the strength of the evidence. Each arrow stimulus was presented for 150 ms and the subjects indicated their choices whenever they felt ready. The maximal length of stimulus sequence was 100. The subjects first took 20 practice trials and then completed a 100 trial session, which typically took less than 20 minutes. We collected data from 26 OCD patients and 23 healthy controls with matching gender, age, and education. Compared with the healthy controls, the OCD group achieved similar accuracy but at longer reaction times and with more accumulated evidence, suggesting that their decision making was less efficient. Interestingly, the anxiety level of the OCD patients, measured with the Hamilton Anxiety Scale, anti-correlated with their performance. The patients with higher HAMA scores had shorter reaction times and steeper psychometric curves, suggesting they were both more accurate and faster. These results suggested the evidence accumulation behavior of the OCD patients might be affected differently by distinguishable components of the disorder.

Disclosures: **Y. Chen:** None. **Y. Liu:** None. **Q. Fan:** None. **T. Yang:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.12/BB55

Topic: H.02. Human Cognition and Behavior

Support: NIH (NINDS-NS078127)
The Sloan Foundation
The Klingenstein Foundation
The Simons Foundation
The McKnight Foundation
The McGovern Institute

Title: Imposing inductive biases to solve general inference tasks in recurrent neural networks

Authors: *R. RAJALINGHAM[1], M. JAZAYERI[2];
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Abstract: A key signature of primate intelligence is the ability to flexibly adapt to novel behavioral demands. In contrast, state-of-the-art deep neural network (DNN) models are notoriously brittle: while they can learn rich domain-specific knowledge via large labeled datasets, DNNs typically require massive amounts of training data, and often do not generalize. It has been hypothesized that the primate brain tackles the problem of generalization by making use of internal models that are capable of simulating external processes in the world. According to this hypothesis, neural network models that are optimized to simulate events and dynamics should be more adept at generalization. We sought to test this hypothesis by training recurrent neural network (RNN) models on a complex dynamic inference task reminiscent of the computer game called Pong.

The objective of the task is to control the vertical position of a paddle to intercept a ball moving across a two-dimensional frame with reflecting walls. Ball movement parameters (initial position, heading, speed) were randomly sampled on every trial. The frame additionally contained a large rectangular occluder right before the interception point such that the ball's trajectory was visible only during the first portion of the trial (prior to disappearing behind the occluder).

The RNNs received a two-dimensional subs-sampled pixel input reflecting moment-by-moment stimuli within the frame, and was trained to generate an output that controlled the vertical position of the paddle. As a first step, we verified that RNNs can learn to simulate the causal structure of this world: RNNs trained to predict key latent variables (ball position x,y) successfully generalized to held-out conditions. Next, we trained RNNs to solve the inference task, i.e. to predict the correct paddle position in order to intercept the ball. RNNs that were jointly optimized to represent the latent variables and intercept the ball could successfully solve this task, generalizing to held-out conditions. In contrast, RNNs that were only optimized for interception were unable to generalize. In other words, imposing an inductive bias mimicking mental simulation of the ball in RNNs was critical to solve this inference task. Finally, comparison of the behavior of RNNs to that of human subjects revealed a quantitative similarity between human and model error patterns. Taken together, these results suggest that imposing suitable inductive biases in RNNs may help uncover how the primate brain implements generalizable internal models.

Disclosures: R. Rajalingham: None. **M. Jazayeri:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.13/BB56

Topic: H.02. Human Cognition and Behavior

Support: The Sloan Foundation

The Klingenstein Foundation
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The McGovern Institute
NEI RO1 (EY023322)

Title: Rapid confidence-based hierarchical and counterfactual reasoning in humans

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Abstract: A defining feature of human cognition is the capacity to process information hierarchically. This is evident in a wide range cognitive tasks such as language processing and intuitive physics. Recent experiments have used multi-stage decision-making tasks to highlight the role of confidence in hierarchical reasoning. Here, we used a novel task demanding multiple rapid and hierarchically organized decisions to further characterize the computational role of confidence in hierarchical and counterfactual reasoning.
Subjects had to track a ball mentally as it moved behind multiple occluded segments of an H-shaped maze (H-maze). At the beginning of each trial, the ball moved visibly down a vertical path towards its intersection with the horizontal segment of the H-maze. Immediately after reaching the H-maze, the ball was made invisible and changed direction toward the left- or right-end of the horizontal segment. After reaching the second branching point, the ball changed direction and moved toward the top or bottom of the vertical segment. After reaching one end of the vertical segment, subjects were asked to choose the point from which they thought the ball would exit the H-maze. To help subjects track the invisible ball, we played three auditory cues, one when the ball reached the horizontal segment, one when it reached the vertical segment, and one when the ball exited the H-maze. To create a challenging inference task, we varied the lengths of the three segments of the H-maze and the speed of the ball on a trial-by-trial basis. To perform the task, subjects had to use the geometry of the H-maze to choose the composite path that was most consistent with the intervals between consecutive auditory cues. Subjects received a binary feedback at the end of each trial.
We analyzed responses in relation to three models, one that relied on joint probabilities over multiple segments (i.e., not hierarchical), one that reasoned hierarchically, and one that used both hierarchical and counterfactual reasoning. Results provided strong evidence for the third model: subjects inferred the position of the ball hierarchically and used their confidence to consider counterfactual possibilities. Consistent with these finding, subjects' reaction times were significantly longer when counterfactual reasoning was warranted. Finally, eye-tracking data both during the ball movement and after the binary feedback exposed the dynamics of subjects' hierarchical and counterfactual reasoning on a trial-by-trial basis. Together, our behavioral and modeling results provide a quantitative account of the role of confidence in hierarchical and counterfactual reasoning during cognitive inference.

Disclosures: **M. Ramadan:** None. **M. Jazayeri:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.14/BB57

Topic: H.02. Human Cognition and Behavior

Support: MOST Taiwan, 107-2410-H-010 -003 -MY3
MOST Taiwan, 104-2410-H-010 -002 -MY3

Title: The role of information lifespan and rate of information flow on decision making

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Abstract: In many decisions we face, collecting more information is beneficial but comes at a cost of time and energy that can otherwise be spent on alternative actions that are equally – if not more – rewarding. Previously, we had shown that people tend to collect less information than they should in a task where information accumulates over time while the size of potential reward for making a correct decision decreases over time. It remains unclear, however, why people exhibit such suboptimal behavior. In this study, using the same task, we investigated two potential causes of suboptimality – information lifespan and rate of information flow.
Method. We examined the role of information lifespan by manipulating the amount of time a piece of information, once presented, stayed on the computer screen (0.2 sec, 0.5 sec, 2 sec and "always on"), while controlling for rate of information flow (20 Hz). We examined the rate of information flow by manipulating how fast a new piece of information is presented – 10 Hz, 20 Hz and 30 Hz – while controlling for information lifespan (always on). As a result, there were 6 conditions, with each condition having 20 participants in a between-subject design.
Results. We replicated previous findings by showing that subjects collected less information than they should have. Rate of information flow did not affect this pattern of suboptimal behavior, but information lifespan did – the shorter a piece of information stayed on the screen, the longer the subjects waited to collecting more information. This suggests that increasing the cost of integrating information over time, elicited by decreasing information lifespan, may promote optimal information collection in decision making.

Disclosures: Y. Liu: None. **S. Wu:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: H.02. Human Cognition and Behavior

Support: Irish Research Council GOIPD/2017/1261
Science Foundation Ireland 15/CDA/3591

Title: Dynamic value biases in decision making under time pressure

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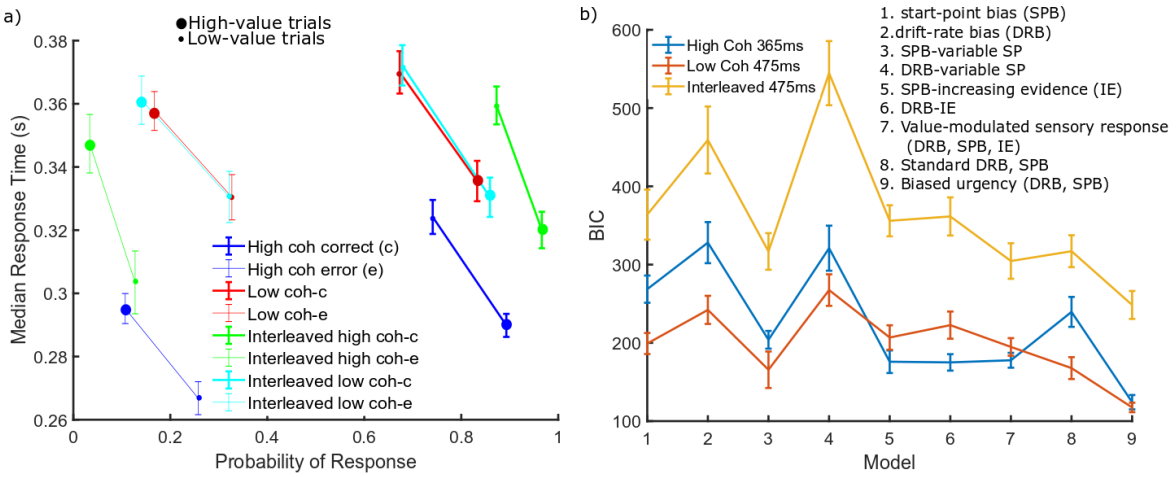
Abstract: In sequential sampling models, value biases in perceptual decisions are usually explained by a shift in starting point (SP) of evidence accumulation. In recent work, additional dynamic biases were needed to explain both behaviour and electrophysiology (EEG) in rapid colour discrimination (Afacan-Seref et al., 2018). Their data were well-described by a model with biases exerted on sensory evidence that increases over time, allowing the accumulator to shift from value to evidence driven over the course of the decision. Here we examined the role of drift rate (DR) and SP biases in a broader range of contexts to see if the findings generalized beyond perceptually easy rapid discrimination. We varied the difficulty of random dot motion direction discrimination in 3 conditions (high coherence, 365ms deadline; low coherence 475ms deadline; interleaved low and high coherence, 475ms deadline). We recorded EEG from 14 participants who were asked to maximise points when the value of each direction (30/10) was cued on a trial-by-trial basis. Responses were significantly faster and more accurate for high value trials (a, all $p<.03$).
We compared average BIC for several models with DR and SP biases and static or increasing evidence for each condition (b, models 1-8). Using Monte-Carlo simulations we minimized the G^2 between the simulated and real response time quantiles for correct and error high and low value trials. As in the colour task, the high-coherence data were best fit by models with increasing evidence. However, this may not be an appropriate model of sensory evidence in longer-timescale decisions, and the low-coherence condition was best fit by a model with static evidence and a biased variable SP. We then tested an alternative mechanism for the shift from value to evidence-driven accumulation—biased dynamic urgency initiated before evidence accumulation (with onset time free to vary). Such a model effectively incorporates both types of bias and provided the best fit of the data across all conditions (model 9). Future work will consider the electrophysiology in parallel with modelling results.



Disclosures: **E.A. Corbett:** None. **A. Martinez Rodriguez:** None. **L. Spence:** None. **C. Judd:** None. **R.G. O'Connell:** None. **S. Kelly:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.16/BB59

Topic: H.02. Human Cognition and Behavior

Title: Relationship between obesity dieting success and measures of decision-making

Authors: K. ALSTATT[1], T. HUYNH[1], A. O'DONOVAN[2,3,4], S. V. ABRAM[5], ***N. C. SCHMITZER-TORBERT**[1];
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Abstract: Obesity is associated with increased discounting of future monetary rewards, suggesting that altered decision-making may contribute to the risk for obesity. Here we examined the relationship between measures of decision-making, obesity and dieting success using an online sample (Amazon's Mechanical Turk service) and an undergraduate male sample. Participants completed monetary or food-based delay-discounting surveys, and a set of experiential foraging tasks (the Movie Row and Candy Row tasks). Rodent versions of the foraging tasks have also been used to demonstrate specific deficits in decision-making in drug-abstinent mice. In the foraging tasks (Movie Row and Candy Row), participants navigated

through a 3D virtual environment on a square track. Rewards (4-sec video clips displayed on a virtual movie screens in the Movie Row task or candy/snacks delivered to magazine for the Candy Row task) were available from four zones on the track. Only a subset of undergraduates completed the Candy Row task. As participants arrived at a zone, the reward category and a random delay were presented. Participants could accept the offer or move on to the next reward site. Behavior on the Candy Row task (using physical rewards) was similar to that of the Movie Row tasks (using videos as rewards), suggesting that these two versions of the task were sensitive to individual differences in rewards. Performance on the monetary and food-based versions of the delay-discounting measure were also positively correlated, but delay discounting measures were not well related to measures from the foraging tasks.
Obesity (determined from self-reported weight and height) was not related to delay discounting measures (k) for money or food, or to the number of rewards earned on the foraging tasks and delay thresholds (how long participants were willing to wait for a reward). Exploratory analyses found that obesity was associated with reduced regret on the Movie Row task. Self-reported change in body mass index (BMI) over the previous year was related to reported use of several dieting strategies (such as attempting to consume less food, avoiding carbohydrates), but not to measures of delay-discounting. However, several dieting strategies interacted with the discounting rate (k). Among participants who reported that they had attempted to eat less food to manage their weight, only participants with low discounting rates showed a reduction in BMI, while for participants who did not report using this strategy, there was no relationship between k and changes in BMI. These results suggest that obesity and dieting success may be related to several different disruptions in decision-making systems.

Disclosures: K. Alstatt: None. **T. Huynh:** None. **A. O'Donovan:** None. **S.V. Abram:** None. **N.C. Schmitzer-Torbert:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.17/BB60

Topic: H.02. Human Cognition and Behavior

Title: Long term effects of nucleus accumbens deep brain stimulation reveal a causal contribution of ventral striatum to human self control

Authors: *B. J. WAGNER[1], C. B. SCHÜLLER[2], T. SCHÜLLER[2], J. BALDERMANN[2], D. HUYS[2], J. PETERS[3], J. KÜHN[2];
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Abstract: Multiple neural systems contribute to self-control in humans (Peters & Büchel 2011) including prefrontal networks involved in cognitive control, and regions of the mesolimbic and mesocortical dopamine system. Early studies on self-control mechanisms focused on characterizing potentially dissociable striatal and prefrontal value signals during inter-temporal choice (Kable and Glimcher 2007) a core behavioral maker of self-control impairments with high long-term stability (Kirby 2009). This debate has ultimately led to a revised view of self-control, according to which (lateral) pre frontal cortex (PFC) exerts top-down control over ventromedial PFC in support of self-controlled choices (Hare et al. 2009; Figner et al. 2010). However, despite the findings of that both striatal reward responses and cortico-striatal connectivity are robustly associated with temporal discounting in cross-sectional analyses, this model is largely silent with respect to the unique contribution of the ventral striatum. We directly addressed this issue by capitalizing on a rare opportunity to longitudinally follow n=7 patients who underwent deep brain stimulation (DBS) to nucleus accumbens for treatment-resistant obsessive-compulsive disorder (OCD). Patients underwent a standard delay discounting paradigm prior to-, after 6 months of continuous DBS and when DBS was turned off for one week. We analyzed subjects' choices using a hierarchical Bayesian modelling approach that accounts for the within-design of the data via JAGS (Plummer, 2003). 5 out of 7 patients showed increased choice impulsivity after 6 months of continuous DBS. Effects were quantified by examining the 95% highest density intervals of each patient's discount-parameter as well as of the corresponding hyperparameter distributions of all three conditions. Our results indicate a unique contribution of the ventral striatum to choice impulsivity in the face of reward availability.

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Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

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Topic: H.02. Human Cognition and Behavior

Support: NIH/NIA R56 AG061888

Title: The dynamics of explore-exploit decisions reveals a signal-to-noise mechanism for random exploration

Authors: *S. F. FENG[1], S. WANG[2], S. C. ZARNESCU[2], R. C. WILSON[2];
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Abstract: When choosing classes for college, should you exploit the Psychology class you are sure to ace, or explore the Photography class you know less about? Exploiting the Psych class is the way to a 4.0, but exploring Photography could be the path to a better life. As with choosing classes in college, making optimal explore-exploit decisions is hard --- explore too much and you'll never major in anything, exploit too much and you might end up on the wrong path. This difficulty arises from the fundamental computational properties of explore-exploit problems: to make an optimal decision we need to consider all possible futures out to some time horizon, but simulating and optimizing over all possible futures is beyond what any brain can do. Work in machine learning has identified a number of heuristics that solve explore-exploit problems well in practice. These heuristics include an explicit bias for information ("directed exploration") and the randomization of choice ("random exploration"). Recent work in Psychology suggests that people actually use directed and random exploration, becoming more information seeking and more random in their responding when they have more opportunity to explore. In this work we focus on random exploration asking, in particular, how can behavioral variability be controlled by the brain? By modeling the explore-exploit choice using a drift diffusion process, we identify two distinct mechanisms by which behavioral variability could be controlled, and by fitting the diffusion model to human behavior, we determine which of these mechanisms humans actually use. More specifically, when applied to an explore-exploit choice, the drift diffusion model assumes that the decision is made by accumulating a noisy value based signal towards one of two bounds: one for explore and one for exploit. Behavioral variability can then be controlled by two different parameters: the signal-to-noise ratio of the accumulation process ("drift rate") and the separation between the decision bounds ("threshold"). By fitting humans' choices and reaction times in a popular explore-exploit task (the Horizon Task, Wilson et al. 2014) we find that while, statistically, both drift rate and threshold change as people have more opportunity to explore, numerically, it is the change in drift rate that has the main effect on random exploration. The provides evidence that random exploration is primarily driven by changes in the signal-to-noise ratio with which reward information is represented in the brain.

Disclosures: **S.F. Feng:** None. **S. Wang:** None. **R.C. Wilson:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

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Topic: H.02. Human Cognition and Behavior

Support: NIH T32 DA041349 (LPS)
NIH 5KL2TR00142 (KTK)
NIH P50 DA006634 (KTK)
Wake Forest School of Medicine

Title: Momentary changes in subjective feelings during conscious decision-making are explained by actual and counterfactual rewards and punishments

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[1]Neurosci. Grad. Program, [2]Physiol. and Pharmacol., [3]Neurosurg., Wake Forest Univ. Sch. of Med., Winston-Salem, NC

Abstract: What would you have done differently this week, and what might have changed as a result? Humans learn from experience by not only considering what rewards or punishments follow from their actions, but also by generating counterfactual thoughts (i.e., "what might have been") to evaluate alternative versions of past events (1). Humans compare actual and counterfactual information to improve decision-making by weighing both actual outcomes and foregone (counterfactual) actions in determining the relative values of different behavioral strategies. Recent evidence suggests that adaptive choice behavior may involve computing values of foregone actions in addition to computing values of chosen actions as predicated by temporal difference reinforcement learning (TDRL) theory (2,3). Indeed, sub-second measurements of dopamine (DA) release in human striatum (4) reveal that DA fluctuations combine reward prediction errors (RPEs) with counterfactual prediction errors (3), which represent how much better or worse an outcome could have been. This superposition of "actual" and "possible" outcomes is consistent with how humans should "feel" about their actions - "missing out" on an experience may elicit a sense of relief or regret depending on the outcome of the event in question. It remains unknown how humans combine actual and counterfactual rewards and punishments when evaluating their momentary subjective experience. To this end, human participants (n=51) completed a two-choice probabilistic reward/punishment task while reporting how they felt about recent outcomes. We employed a TDRL algorithm (Q-learning, 5) to model the series of participants' actions and outcomes to determine how participants assign value to different choices available in the task. We used these learned action values to construct a set of models that assessed the influence of actual and counterfactual rewards and punishments on self-reported feelings. Scoring the models across subjects by their Bayesian Information Criterion (BIC, 6) revealed that momentary changes in feelings are best explained by the combined influence of recent outcomes, expected values of chosen actions, and expected values of foregone (counterfactual) actions. In sum, our analysis shows that humans combine actual and counterfactual information when evaluating their moment-to-moment feelings, as opposed to using factual information alone. Our future directions include investigating the neural basis of counterfactual thinking and associated subjective feelings using noninvasive (fMRI and MEG) and invasive (human voltammetry) measurements of brain activity during conscious decision-making.

Disclosures: L.P. Sands: None. **A. Jiang:** None. **K.T. Kishida:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.20/BB63

Topic: H.02. Human Cognition and Behavior

Title: The influence of action on explore-exploit decisions

Authors: *S. WANG, H. SADEGHIYEH, R. C. WILSON;
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Abstract: When deciding what to eat, will you order the pizza you always like or the new pasta on the menu? The tradeoff between exploiting the option you know and exploring new options is known as the explore-exploit dilemma. How far ahead one plans for the future, the "horizon", plays a key role in making such explore-exploit decisions. You will be more likely to try the new pasta if you know you are returning to the same restaurant again. Previous work has shown that humans can adapt the level of exploration to the horizon context (Wilson et al 2014). In this work we used a modified version of the same task to show that this horizon-adaptive exploration depends critically on how the value information is obtained.

In the original task, participants are instructed to choose between two one-armed bandits that give out random rewards from different Gaussian distributions whose means are initially unknown. Sometimes, they need to make 1 choice (short horizon) and sometimes 6 choices (long horizon). To give participants some information about the relative value of the two bandits before they make their own decisions, in the original task, participants are instructed to press the arrow keys according to a preset sequence to reveal some sample outcomes from the two bandits - these are referred to as "sample plays". After the sample plays, in their first free choice, people are more biased towards less-known option (known as directed exploration) and behave more randomly (known as random exploration) in longer horizon (Wilson et al 2014).

In our modified version, instead of actively pressing arrow keys to reveal the outcomes of the sample plays, all of the sample outcomes are presented passively to participants without key press. In this Passive condition, people show no horizon dependent directed or random exploration. This is true even if the same participant has played the Active version, i.e. the original Horizon Task, first.

To further investigate what kills the horizon-adaptive exploration in the passive condition, we performed a series follow up experiments in which: (a) the outcomes of sample plays were shown to people sequentially without a key press, and (b) outcomes of sample plays were revealed upon pressing a neutral key (space bar) instead of the arrow keys. In neither case did we find evidence for horizon-adaptive exploration. This suggests that the same information obtained by pressing the arrow keys which corresponds to the two options is registered differently than if obtained by pressing a neutral key or without key press. This work reveals a more complicated

nature of explore-exploit decisions and suggests the influence of action on how subjective utility is computed in the brain.

Disclosures: S. Wang: None. **H. Sadeghiyeh:** None. **R.C. Wilson:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.21/BB64

Topic: H.02. Human Cognition and Behavior

Support: NIDA Grant DA043676

Title: Interactions between opioid craving and impulsive decision-making: Behavioral and neural evidence

Authors: *S. LOPEZ-GUZMAN[1,2], A. B. KONOVA[2,4], K. LOUIE[2], N. V. BANAVAR[2], A. BELL[2,3], J. ROTROSEN[3], P. W. GLIMCHER[2,3];
[1]Univ. del Rosario, Bogota, Colombia; [2]Ctr. for Neural Sci., [3]Langone Sch. of Med., New York Univ., New York, NY; [4]Brain Hlth. Inst., Rutgers Univ., Piscataway, NJ

Abstract: Objective: Individuals with addictions are widely reported to be highly impulsive. While impulsivity is often thought of as a personality trait, this psychological construct entails many dimensions which may not all be fixed. Impulsive choice for instance, often studied via economic models of intertemporal choice, is the result of a neural value computation subject to poorly understood contextual modulation from external and internal signals. How does craving for drugs, for example, precipitate changes in decision-making that lead to reuse, relapse, and risk of overdose? Understanding how varying internal states like craving affect impulsive decision-making could be of significant clinical value. To address this, we followed a cohort of patients with Opioid Use Disorder (OUD) receiving treatment. We recorded variations in symptoms and changes in choice impulsivity with repeated sessions of a temporal discounting (TD) task. Patients also underwent the task in the fMRI scanner. This longitudinal approach allowed us to follow their dynamics in symptomatology, drug use, and impulsivity and test how these relate to neural measures.
Methods: 74 patients with OUD underwent 15 testing sessions over the course of 7 months after treatment initiation. Each session consisted of an symptomatology assessment (craving, pain, withdrawal, and anxiety), an incentive-compatible TD task (where participants chose between real immediate and delayed monetary rewards), and a drug use evaluation (by self-report and toxicology). 52 matched community controls (CC) performed similar sessions for a total of 5 visits. A subset of both OUD and CC participants performed the TD task in the fMRI scanner.
Results: Behaviorally, we found the TD task's discount rate to be more variable over time in the

OUD than in the CC group. This variability in OUD patients was in fact time-locked to changes in craving levels such that recent increases in craving (past 7 days) were predictive of increased impulsive decision-making (a steepening of the monetary discount curve.) Both craving and increased impulsivity contributed to predicting imminent opioid use events. Neurally, OUD patients with higher craving levels before the fMRI scan showed increased activity during the decision period of the TD task in a network of areas consisting of parietal association cortex and anterior insula. We hypothesize that craving, through its representation in proprioceptive and interoceptive cortex, affects decision making about future rewards. Next steps include exploring the interaction between areas like insula and subjective value representation in the ventral striatum and ventromedial prefrontal cortex.

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Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

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Program #/Poster #: 518.22/BB65

Topic: H.02. Human Cognition and Behavior

Title: Large-scale brain oscillatory network dynamics of perceptual decision-making: An EEG study

Authors: *S. GHIMIRE, M. DHAMALA;
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Abstract: Large-scale brain networks are believed to be involved in perceptual decision-making processes. Even though the dynamics of few brain areas in these networks are studied for their role in multi-step subprocesses, from sensory input to a perceptual decision and to a motor response, large-scale networks across the whole brain and their spatiotemporal oscillatory dynamics remain to be fully understood. In this study, using human scalp electroencephalography (EEG) recordings combined with source reconstruction techniques, we study how network oscillations functionally organizes all the Broadman areas and what temporal sequence of events in interactions occur during a face-house perceptual decision-making task. Each of these regions included multiple voxels. Single task trials of 26 participants were used to reconstruct source signals on those voxels and the singular value decomposition was used to estimate the representative orientation for dipoles in those voxels in each Broadman area. Spectral interdependency analysis showed that network oscillations in different frequency bands link many of these distributed areas during the task. Measures of network activity from the frontoparietal network were correlated with behavioural performance. These findings of whole-

brain network oscillations and timings of their peak activities broaden our understanding of the local and large-scale subprocesses leading to perceptual decisions.

Disclosures: **S. Ghimire:** None. **M. Dhamala:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: H.02. Human Cognition and Behavior

Support: This study was supported by Brain/MINDS from AMED under Grant Number JP18dm020700 and JSPS KAKENHI Grant Number JP18H05432.

Title: A Bayesian model explains intentional binding as precision-dependent, causality-based cue integration

Authors: *R. LEGASPI, T. TOYOIZUMI;
Neural Computation and Adaptation, RIKEN Ctr. for Brain Sci., Wakoshi, Japan

Abstract: Although Bayesian cue integration was proposed as a general principle behind sense of agency (SoA) (Moore & Fletcher, 2012), it was unknown if intentional binding experiments are consistent with Bayesian principles, and if indeed, the question is how. For example, it was pointed out that only indirect empirical evidence existed in support of Bayesian integration (Moore & Fletcher, 2012) and that Bayesian integration does not explain outcome binding (Wolpe et al., 2013). The fact that SoA, i.e., the feeling that we chose and intended an action that caused an external outcome (Haggard, 2017), is phenomenologically thin makes it hard to measure (Moore, 2016). However, intentional binding provides a robust implicit measure of SoA (Moore & Obhi, 2012): the time interval between an action and its sensory outcome is perceived to compress when the action is intentional and repulse when involuntary. We have introduced a Bayesian model that explains how action and outcome signals, in isolation or interacting with each other, may underlie SoA (Legaspi & Toyoizumi, SfN 2018). However, we have yet to propound specific predictions by our model on intentional binding.
Our Bayesian model accounts for the intentional binding effects reported by Haggard et al. (2002) and Wolpe et al. (2013). Specifically, our model judges the causation of the outcome by the action in both the binding and repulsion effects reported by Haggard et al. This means that causality is perceived regardless of whether the action is self-generated or unintended. However, binding happens when sensory signals are reliable (precise), hence, not by perceiving causation alone. Secondly, our model explains outcome binding in terms of cue-reliability that Wolpe et al. considered as non-Bayesian. As a consequence, our model gives two distinct testable predictions for future experiments on SoA: (1) perceptual binding or repulsion happen on a per-trial basis

and must correlate with the estimated causality between action and outcome, yielding a bimodal distribution of the perceived action-outcome interval that reflects the presence and absence of SoA, and (2) experimental manipulations that reduce the unreliability of sensory inputs would increase SoA even for unintended actions.

Disclosures: R. Legaspi: None. **T. Toyoizumi:** None.

Poster

518. Human Decision-Making and Reasoning: Cognition and Computations I

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 518.24/BB67

Topic: H.02. Human Cognition and Behavior

Support: MOST Taiwan, 104-2410-H-010 -002 -MY3
MOST Taiwan, 104-2410-H-010 -002 -MY3

Title: Context effects on probability estimation

Authors: *S.-W. WU[1], W.-H. LIN[2], J. L. GARDNER[3];
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Abstract: Many decisions we face rely on how we perceive potential outcomes associated with options under consideration and estimate their corresponding probabilities of occurrence. Decades of research from psychology indicate that outcome evaluation is subjective and context-dependent. However, despite its subjective nature, it remains unclear whether probability estimation is context-dependent. The purpose of this study therefore was to investigate how contexts impacts probability estimation at the behavioral and computational and neural implementation levels.
Method. In a simple stimulus-reward associative learning task, human subjects were asked to estimate probability of reward associated with visual stimuli. On each trial subjects saw a stimulus and had to estimate its probability of reward. After estimation, a feedback on whether they won a reward was provided. At the beginning of the experiment, subjects did not know the probabilities but can learn through feedback over the course of the experiment. Context was established by pairing two stimuli each carrying a unique probability of reward in a block of trials such that they appeared in random order. To investigate context effect, for a given probability of reward, we assigned two stimuli to it. These two stimuli were separately assigned to two different contexts where the reward probability of the other stimulus differed. A total of 4 behavioral experiments and one fMRI experiment were carried out so as to investigate the full dynamic range of probability.
Results. We found that probability estimation is context-dependent. Probability estimate of a

stimulus was affected by the reward probability of the other stimulus present in the same context such that it was biased away from the reward probability of the other stimulus. Further, the magnitude of such context effect appeared to be scaled by the estimated outcome uncertainty associated with the stimulus. Multivoxel pattern analysis on fMRI data revealed that dorsal anterior cingulate cortex and ventromedial prefrontal cortex – two regions implicated in uncertainty coding and valuation –represented context effect on probability estimate. Together, these results provide insights into the computational building blocks and neural mechanisms for probability estimation.

Disclosures: S. Wu: None. **W. Lin:** None. **J.L. Gardner:** None.

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.01/BB68

Topic: H.03. Schizophrenia

Support: EU Marie Skodowska-Curie grant agreement No 734227

Title: Have you seen the ghost - Saccadic suppression in schizophrenia

Authors: *R. LENCER[1], I. MEYHOEFER[1], J. TRIEBSCH[2], K. SILLING[1], T. WATSON[3], M. LAPPE[2];
[1]Dept. of Psychiatry and Psychotherapy, [2]Inst. for Psychology, Univ. of Muenster WWU, Muenster, Germany; [3]Sch. of Social Scienes and Psychology, Western Sydney Univ., Sydney, Australia

Abstract: About 40% of patients with schizophrenia report discrete disturbances of visual perception, e.g. pseudo-movements of objects, which do not fulfil the criteria of hallucinations but nonetheless impact patient's well-being in daily life. One reason may be an impairment in saccadic suppression, the removal of disturbing visual input provoked by high saccade velocities up to 700°/s. Saccadic suppression can be understood as a reduction of visual sensitivity during saccades. Whether saccadic suppression is impaired in patients with schizophrenia has not been studied systematically. 17 patients with schizophrenia (mean 35.7 years) and 18 healthy controls (mean 34.2 years) performed 200 reflexive saccade trials with targets being apart by 7°. While saccades were in flight a Gabor stimulus (the "ghost") occurred for 11ms halfway (3.5°) to the target. After the saccade participants were asked to indicate whether they had seen the "ghost" by a button press. Prior to the experiment, Gabor contrasts were adjusted to 90% correct thresholds during fixation in each participant. Eye movements were recorded at 500 Hz. As expected, visual disturbances were present in patients but not in healthy controls ($p<0.01$). However, ghost detection rates were similar in both groups with saccadic suppression occurring between +/-

50ms around saccade onset, as typically observed with this task. Higher saccadic suppression rates were related to larger saccade amplitudes and shorter saccade latencies in both groups. Groups only differed on saccade amplitude, being smaller in patients (p=0.012). Patients' saccadic suppression performance was unrelated to symptom expression or dosage of antipsychotic medication. The finding of unimpaired saccadic suppression in patients bears important implications regarding basic visual information processing in schizophrenia. Saccadic suppression has been proposed to rely on the efference copy of the motor command indicating saccade onset as well as on backwards masking. Our present findings suggest both mechanisms are sufficiently intact in patients, as required for unimpaired saccadic suppression, and are unrelated to visual disturbances.

Disclosures: R. Lencer: None. **I. Meyhoefer:** None. **J. Triebsch:** None. **K. Silling:** None. **T. Watson:** None. **M. Lappe:** None.

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.02/BB69

Topic: H.03. Schizophrenia

Title: Opioid antagonists are effective treatments for the symptoms of schizophrenia: A meta-analysis

Authors: *S. CLARK[1], J. VAN SNELLENBERG[2], J. M. LAWSON[3], A. ABI-DARGHAM[2]; [1]Terran Biosci. Inc, New York, NY; [2]Psychiatry & Behavioral Hlth., Stony Brook Med., Stony Brook, NY; [3]Neurosci., Columbia Univ. Med. Ctr., New York, NY

Abstract: Importance: Current treatments for the symptoms of schizophrenia, are only effective for positive symptoms in some individuals, and have considerable side effects that impact compliance. Thus, there is a need to investigate the efficacy of other compounds in treating both positive and negative symptoms. **Objective:** To conduct a meta-analysis to determine whether pan-opioid antagonists have therapeutic efficacy in patients with schizophrenia. **Data Sources:** Online databases Ovid Medline and PsychINFO, PubMed, EMBASE, Scopus, Cochrane library/CENTRAL, Web of Science, and Google Scholar from 1970 through Feb 2019, all of the bibliographies in identified trials, and a journal search. **Study Selection:** English language randomized placebo-controlled clinical trials of naloxone, naltrexone, nalmefene, and buprenorphine in patients with schizophrenia, that measured drug effects on positive, negative, or total symptoms. **Data Extraction and Synthesis:** Following PRISMA guidelines data were extracted from manuscripts with the following priority: means and SDs, test statistic (t or F), P value, means and SDs or raw data estimated from figures, an in-text description of whether the findings were statistically significant, an in-text description of the direction of effect. **Main**

Outcomes and Measures: Primary study outcomes were the within-subject change on any symptom assessment scale for positive, negative, or general symptoms of schizophrenia between active drug and placebo conditions. **Results:** Twenty nine studies were included. We found a significant effect of all drugs on total symptoms with both the random effects model: (g = 0.29; P = 0.024; k = 21) and the bootstrap effects model: (g = 0.26; P = 0.001; k = 29) and a significant effect on total scales (g = 0.25288; P < .0001; k = 18). We also observed a significant effect of all drugs on all positive scales combined with both the random effects model: (g = 0.37; P = 0.012; k = 17) and the bootstrap model (g = 0.3325; P < .0001; k = 21). **Conclusions and Relevance:** This evidence provides support for further testing in randomized clinical trials of a new class of non D2 receptor drugs, based on opioid mechanisms, for the treatment of positive and negative symptoms of schizophrenia.

Disclosures: **S. Clark:** A. Employment/Salary (full or part-time):; Terran Biosciences Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Terran Biosciences Inc.. **J. Van Snellenberg:** None. **J.M. Lawson:** None. **A. Abi-Dargham:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Terran Biosciences Inc..

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.03/BB70

Topic: H.03. Schizophrenia

Support: National Key R&D Program of China (2017YFC1310400)
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National Natural Science Foundation (81571300, 81527901, 31771174)
Natural Science Foundation and Major Basic Research Program of Shanghai (16JC1420100)

Title: Perceived speed of illusory rotation for the Pinna Brelstaff Figure is linked to schizophrenia symptom severity

Authors: K. ZELJIC[1], Q. XIANG[2], Y. PAN[2], D. LIU[3], *Z. WANG[1];
[1]Inst. of Neurosci., Shanghai, China; [2]Shanghai Mental Hlth. Ctr., [3]Shanghai Key Lab. of Psychotic Disorders, Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China

Abstract: Motion perception deficits are a core perceptual impairment in schizophrenia. While their pathophysiology is unclear, psychophysical reports suggest aberrant motion integration at global rather than local processing stages, implicating extrastriate neural substrates medial superior temporal area (MST) and middle temporal area. However, to date, global motion integration in schizophrenia has only been studied using simple translational motion. Whether similar deficits exist in the integration of complex-flow motion such as real and illusory rotation is unknown. We recently showed that the Pinna-Brelstaff figure (PBF) can be physically manipulated to elicit such motion, which is encoded in MST, and can be parametrized to quantify perceptual variability in healthy subjects (Pan et al., 2016, Wang et al., 2016). Here, we use this stimulus and a modified illusion-free PBF to probe how individuals with schizophrenia perceive illusory and real complex-flow patterns. Data were collected from 102 schizophrenia patients and 90 controls, with simultaneous eye tracking also performed to monitor potential effects of eye movement on task performance. Schizophrenia symptoms were evaluated with the Positive and Negative Syndrome Scale. To quantify illusory perception strength, we use a previously validated nulling procedure in which the shift of the psychometric function corresponds to the illusory rotation induced by the expanding PBF (Luo et al., 2019). We found no significant group differences in perception of real rotation ($p>0.5$). However, perceived illusory strength was significantly lower in patients ($p<0.05$). For eye movement, patients had a significantly lower fixation count and fixation duration, and a significantly higher saccade count, although we found no effect of these on task performance. Interestingly, there was a significant effect of positive symptoms on perceived illusory strength in patients, which was mediated by angular speed of the PBF on the retina. Our preliminary results suggest that schizophrenia is characterized by alterations in global motion integration of complex illusory stimuli. Furthermore, the processes involved in this integration may be linked to those that underlie positive symptoms of this disorder.

Disclosures: K. Zeljic: None. **Q. Xiang:** None. **Y. Pan:** None. **D. Liu:** None. **Z. Wang:** None.

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.04/BB71

Topic: H.03. Schizophrenia

Title: Deficits of multisensory integration in schizophrnenia and autism: Common or specific neural pathways?

Authors: M. TOYMAIAN[1], P. COVANIS[2], A. MANTAS[2], T. KARANTINOS[2], S. KAYAS[3], C. KLEIN[4], ***N. SMYRNIS**[1];
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Mental Health, Neurosciences and Precision Med. Res. Inst. "COSTAS STEFANIS", Athens, Greece; [3]SKKA A LIFEPLAN, Athens, Greece; [4]Child and Adolescent Psychiatry, Univ. of Freiburg Med. Sch., Freiburg, Germany

Abstract: Complex decision making relies on the successful integration of sensory information from different modalities named Multi Sensory Integration (MSI). Evidence for deficits in MSI has been documented in autism spectrum disorder (ASD) and less so in schizophrenia (SZ). A target detection task with audio (A), visual (V) and audiovisual (AV) stimuli to examine the behavioural and neuropshysiological indices in MSI comparing these two neurodevelopmental disorders. 31 healthy controls (HC), 32 SZ patients and 19 ASD patients performed the task while Reaction times (RT) and scalp recorded electrophysiological (EEG) activity were measured. All groups had significantly faster RTs ($F_{2,82} = 4.33$, $p = 0.02$) and higher RT variability ($F_{2,82} = 51.9$, $p = 0.00001$) in the AV condition, with the SZ group showing the slowest reaction times ($F_{4,164} = 3.82$, $p = 0.005$) and highest reaction time variability (RTV) ($F_{4,164} = 3.39$, $p = 0.01$). We applied a novel bootstrap method to confirm the presence of true MSI for each subject. Application of this method confirmed the presence of MSI in 77% of HC, 47% of SZ patients and 16% of ASD patients ($F_{2,79} = 11.35$, $p < 0.0001$). At the neural level, we compared two auditory (N1, P2) and two visual (P1, N2) ERP's. All four components were larger in the Av compared to the corresponding A and V conditions. The control group showed significant enhancement of the auditory **N1** amplitude in the AV condition compared to the SZ group, while the N1 amplitude of the ASD group was between that of the other two groups ($F_{2,79} = 3.5$ $p = 0.03$). The auditory **P2** peak latency was faster in the AV condition compared to the A condition only for HC while patients with SZ and ASD showed the reverse effect ($F_{2,79} = 5.83$, $p = 0.004$). The visual P1 peak latency was slower for the AV condition compared to the V condition only for the ASD patient group ($F_{2,79} = 5.09$, $p = 0.008$). Importantly these effects did not correlate with the presence of MSI in all groups. These results show a complex relation of MSI deficits with sensory processing of visual and auditory stimuli in schizophrenia and autistic spectrum disorder and suggest the presence of specific neural substrates leading to MSI deficit in each disorder.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.05/BB72

Topic: H.03. Schizophrenia

Title: Testing the brain-heart linkage in schizophrenia and obsessive compulsive disorder: The effect of cardiovascular activity on saccadic eye movement performance

Authors: M. LAZARIDI[1], P. COVANIS[2], G. PANAGIOTAROPOULOU[2], T. KARANTINOS[2], ***C. G. THELERITIS**[1], N. SMYRNIS[1];
[1]Psychiatry, Natl. and Kapodistrian Univesrity of Athens Med. Sch., Athens, Greece; [2]Univ. Mental Health, Neurosciences and Precision Med. Res. Inst. "COSTAS STEFANIS", Athens, Greece

Abstract: The neurovisceral integration model proposes a brain-heart linkage where prefrontal cortical brain areas related to executive functions are connected to midbrain areas that are responsible for the vagal control of the heart. There is evidence documenting autonomic dysregulation among patients with schizophrenia (SZ) while much less is known in patients with OCD. Both SZ and OCD patients present deficits in the inhibitory control of saccadic eye movements related to prefrontal cortical areas. The current study aims to examine the association between autonomic activity and inhibitory oculomotor control in SZ and OCD patients using indexes of heart rate variability (HRV) measured during the performance of saccade and antisaccade tasks. So far accumulated results from 10 healthy controls (HC) and 12 SZ patients confirmed the presence of a deficit in antisaccade task performance in schizophrenia (35% error rate for patients versus 15% error rate for controls, $t = 3.85$, $p < 0.001$) as well as increase in mean reaction time and reaction time variability for both voluntary saccades and antisaccades. Electrocardiographic (ECG) recordings were used in to determine autonomic activity five minutes before (baseline) and five minutes after (recovery), as well as during saccade and antisaccade task performance. RR intervals were detected in the ECG signal and used to measure indexes of sympathetic and parasympathetic activation in both time and frequency domains. Preliminary analysis of the RR intervals confirmed that lower error rate in the antisaccade task positively correlated with time domain measures of parasympathetic activation (root mean square differences between successive RR intervals $r = 0.32$, $p = 0.03$, integral of the RR interval histogram divided by the height of the histogram, $r = 0.31$, $p = 0.03$, and standard deviation perpendicular to the line of identity in Poincare plot, $r = 0.32$, $p = 0.03$) as well as frequency domain measures (high frequency component in power spectrum estimates of HRV, $r = 0.34$, $p = 0.02$). Further increase in sample size of HC and SZ patients as well as inclusion of OCD patients (currently not included in the analysis due to small sample size) will allow the investigation of the interaction of these effects with group to test the hypothesis of between HRV and cognitive control in schizophrenia and obsessive compulsive disorder.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.06/BB73

Topic: H.03. Schizophrenia

Support: NIH MH57440

Title: Differential effects of juvenile or adolescent stress in adult rats: Behavioral manifestation and neurophysiological correlates

Authors: *X. ZHU, A. GRACE;
Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Epidemiology studies overall implicate early-life stress as a risk factor for psychosis in adults. Childhood and adolescence are potential sensitive/critical periods for traumatic experiences. The present study sought to directly compare the vulnerability to the long-term consequence of stress in juvenility or adolescence.Male Sprague Dawley rats were exposed to various stress paradigms during juvenility (PD21-30), adolescence (PD30-40), and adulthood (PD65-74), including daily footshock (FS), occasional restraint stress (RS), and the combination (FS+RS). The long-term (>PD75 & >6 weeks after stress) stress consequence were assessed by (1) *in vivo* recording of dopamine (DA) neurons in the ventral tegmental area (VTA), (2) behavioral assays including elevated plus maze (EPM), novel object recognition (NOR), and amphetamine-induced hyperlocomotion (AIH). In addition, high-frequency stimulation(HFS)-induced medial prefrontal cortex (mPFC) - basolateral amygdala (BLA) circuit plasticity was assessed *in vivo* during development.Combined stress during adolescence increased DA neuron population activity in the VTA, produced persistent anxiety-like behaviors in EPM, deficits in NOR, and increased AIH. Our preliminary data suggested that similar effects were produced by juvenile FS+RS as well. Importantly, while FS or RS alone during adolescence produced long-lasting behavioral effects in NOR and EPM, adult DA-dependent AIH and DA population activity were not affected. This is distinct from that of juvenile stress, as FS alone induced a long-term increase in both DA neuron population activity and AIH, reminiscent of stress vulnerability in rats with mPFC lesion (Gomes et al., 2017). To examine whether the mPFC exerts differential control over BLA across development, HFS-induced mPFC-BLA plasticity was assessed. Preliminary data revealed that the plasticity of juvenile mPFC-BLA circuit is distinct from that of adolescence. Specifically, juvenile HFS produced a trend of increase in spike probability, whereas adolescent HFS produced an adult-like suppression of firing probability in the putative BLA projection neurons. In addition, single-pulse activation of mPFC induced differential latencies of response in the BLA, suggesting a difference in action potential propagation speed likely due to developmental myelination difference. Altogether, our results

suggest juvenile and adolescence represent distinct windows of stress vulnerability. This rapid change of behavioral/neurophysiological vulnerability is potentially mediated by progressive maturation of the mPFC to BLA circuit.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.07/BB74

Topic: H.03. Schizophrenia

Support: NIMH R44 MH091793-03

Title: Computerized social cognitive training for individuals with schizophrenia is associated with neural changes in the theory of mind network

Authors: *S. LOKEY[1,2], K. M. HAUT[3], A. LEE[2], B. GALINDO[2], S. PRIDGEN[2], A. SAXENA[2,5], M. NAHUM[6,7], C. I. HOOKER[4];
[1]Univ. of Illinois at Chicago, Chicago, IL; [3]Psychiatry and Behavioral Sci., [4]Dept. of Psychiatry and Behavioral Sci., [2]Rush Univ. Med. Ctr., Chicago, IL; [5]Univ. of Rochester, Rochester, NY; [6]Posit Sci., San Francisco, CA; [7]Hebrew Univ. of Jerusalem, Jerusalem, Israel

Abstract: Impaired social cognition (SC) in schizophrenia is a deficit that often persists throughout the course of the illness and is a strong predictor of everyday functioning. Functional neuroimaging studies have found that individuals with schizophrenia display lower activation during theory of mind and emotion processing tasks in social brain areas when compared to healthy controls. As a part of a randomized, double-blind, controlled trial to assess the efficacy of SocialVille, a novel, browser-playable treatment program designed to specifically address core SC deficits, we examined the effects of treatment on the underlying neural activity of theory of mind in individuals with schizophrenia. Sixty-four demographically matched participants with DSM-V diagnosis of schizophrenia participated in either SocialVille or active control games, comprising 3-5, 45-minute weekly sessions (~40 sessions) over twelve weeks. Pre- and post-training, subjects completed an untrained theory of mind fMRI task comprising reading vignettes about a person's thoughts (THO), emotions (EMO), or appearance (APP), and judging whether a subsequent action by that person would logically follow the story. Preliminary fMRI results indicate that the contrast hypothesized to be most associated with theory of mind (THO+EMO>APP), activated several regions, most strongly the anterior cingulate cortex and medial frontal gyrus. Additionally, initial whole-brain group analysis of treatment effects suggests that participants in the active training condition significantly increased activity in the

paracingulate gyrus, superior frontal gyrus, and bilateral orbitofrontal cortex, compared to baseline and compared to controls. Overall, these results demonstrate that computerized social cognitive training engages and enhances areas in the theory of mind network. This supports the potential efficacy of computerized training for social cognition deficits in individuals with schizophrenia.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.08/BB75

Topic: H.03. Schizophrenia

Title: Increased functional coupling between VTA and hippocampus during rest in first-episode psychosis

Authors: *D. F. GREGORY[1], M. JALBRZIKOWSKI[2], W. FORAN[2], D. F. MONTEZ[3], B. LUNA[2], V. P. MURTY[1];
[1]Temple Univ., Philadelphia, PA; [2]Univ. of Pittsburgh, Pittsburgh, PA; [3]Washington Univ. in St. Louis, St. Louis, MO

Abstract: The development of psychosis is associated with increases in dopamine (DA) signaling, which have been strongly linked to positive symptoms (Heinz & Schlagenhauf, 2010). This neurobiological marker is present in prodromal individuals prior to the first-episode of psychosis (FEP), suggesting that dopamine-related deficits are core to the disorder's etiology (Howes et al, 2009). Psychosis is also reliably associated with deficits in hippocampal function (van Erp et al, 2015). Animal models have shown a positive-feedback loop between hippocampus and ventral tegmental area (VTA), the source of mesolimbic DA neurons; such that hippocampus regulates tonic VTA activation which can facilitate downstream plasticity within hippocampus (Lisman & Grace, 2005). The methylazoxymethanol acetate (MAM) model, a prominent rodent model of psychosis, suggests that early hippocampal dysfunction causes dysregulation of tonic VTA signaling (Lodge & Grace, 2011). These neurobiological deficits are thought to underlie the positive symptoms seen in psychosis. However, in psychosis, the study of hippocampal deficits and VTA signaling usually occur in isolation (but see Modinos et al, 2015). Importantly, open questions remain whether FEP individuals, who are proximal to the onset of psychosis, show deficits in VTA-hippocampal circuits. Using resting state fMRI (FEP: N=46; controls: N=32), we quantified functional coupling of extracted timeseries of VTA with right and left anterior hippocampus, respectively. We found a significant difference between groups, such that functional coupling between VTA and right anterior hippocampus was greater in FEP versus

controls ($p < 0.05$). A similar non-significant difference was found with left anterior hippocampus ($p = 0.15$). This pattern of results remained consistent when controlling for age and sex. These findings support that VTA-hippocampal circuits differ in FEP, which is consistent with predictions made by the MAM model, and could help provide a putative marker of psychosis risk. Future studies will extend these characterizations of VTA-hippocampal circuits into clinical high-risk populations.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.09/BB76

Topic: H.03. Schizophrenia

Title: Investigation of the temporal dimension of prepulse inhibition of the acoustic startle response

Authors: M. DEBONO, N. PARENTELA, D. BITRAN, *A. C. BASU;
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Abstract: Prepulse inhibition (PPI) of the acoustic startle response is a sensorimotor gating process in which the acoustic startle response is attenuated by pre-presentation of a sub-startle-threshold stimulus. PPI is disrupted in schizophrenia and autism spectrum disorders, and sex differences have been observed in both PPI and the incidence and onset of these disorders. Human and animal studies vary in the testing parameters used to assess PPI, and we believe that these differences may account for some of the inconsistency in results and conclusions drawn from these studies. The current study observes PPI in C57BL/6J mice when the prepulse is presented at 1, 5, 10, 50, 100, 500, and 2000 ms intervals preceding a startle stimulus. Our findings suggest that PPI is a threshold phenomenon with respect to inter-pulse interval, that there are no systematic sex differences in PPI across this temporal range of inter-pulse intervals, and that males may exhibit more variability than females in PPI. As such, these findings may provide insight into the neural mechanisms of PPI, as well as demonstrate a need to assess other relevant biological factors that may contribute to variability in PPI, such as litter effects and social dominance status.

Disclosures: M. DeBono: None. **N. Parentela:** None. **D. Bitran:** None. **A.C. Basu:** None.

Poster

519. Clinical and Biomarker Research in Schizophrenia

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Topic: H.03. Schizophrenia

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PENN (R01-MH65578)
UW (R01-MH65558)

Title: Machine learning approaches to characterize neurophysiological and cognitive measures predictive of schizophrenia diagnosis

Authors: *J. KNICKREHM[1], R. KIM[1], C. LAINSCSEK[1,2], A. L. SAMPSON[1], R. C. GUR[3,4], R. E. GUR[3], T. COGS INVESTIGATORS[5], T. J. SEJNOWSKI[1,2,6], G. A. LIGHT[5,7];
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Abstract: Background: Schizophrenia (SZ) is a debilitating and heterogeneous neuropsychiatric disorder that affects multiple domains of neurophysiologic and cognitive functioning. Although SZ patients have robust impairments across domains, it is not clear which measures are optimally sensitive for correctly classifying SZ patients vs. nonpsychiatric comparison (NC) subjects. Machine learning is a rapidly growing field that allows algorithms to learn and extract salient features from data. The proposed study applied machine learning techniques to a large dataset of SZ and NC participants in order to identify measures that maximally discriminate groups. Methods :The Consortium on the Genetics of Schizophrenia (COGS-2), the largest of its kind, is a multi-center study that assessed Mismatch negativity (MMN) and P3a event related potential amplitudes and the Penn Computerized Neurocognitive Battery (CNB) measures in 877 SZ and 753 NC participants. Cognitive domains included executive control, episodic memory, complex cognition and social cognition. Elastic net regularized regression was first applied to the dataset to identify a subset of the measures most important for classifying SZ participants from NC participants. A multi-layer perceptron (MLP) model was then employed using the identified

features to evaluate classification performance.
Results: The elastic net regularized regression model revealed MMN and P3a as well as CNB measures of working memory (verbal and spatial working memory), executive control (mental flexibility and attention), and complex cognition (spatial ability and emotion identification) significantly contributed to classification. Using these features, an MLP model achieved a high classification accuracy (78.3%; average across 10-fold cross validation accuracy values).
Conclusions: Machine learning approaches identified an optimal set of neurophysiological and neurocognitive measures for identifying participants diagnosed with schizophrenia. Applying similar approaches to other modalities of data, such as imaging and genetic data, could help develop potential biomarker candidates for complex and heterogeneous psychiatric disorders.

Disclosures: J. Knickrehm: None. **R. Kim:** None. **C. Lainscsek:** None. **A.L. Sampson:** None. **R.C. Gur:** None. **R.E. Gur:** None. **T. COGS Investigators:** None. **T.J. Sejnowski:** None. **G.A. Light:** None.

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.11/BB78

Topic: H.03. Schizophrenia

Support: R01MH107558
K01DA043615

Title: Mismatch negativity deficits in individuals at clinical high risk for psychosis

Authors: *R. B. SHAIK[1], M. A. PARVAZ[1], Z. BILGRAMI[1], C. SARAC[1], C. BENAVIDES MARTINEZ[1], J. LOPEZ CALDERON[2], C. CORCORAN[1];
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Abstract: BACKGROUND: Sensory processing deficits are core features of schizophrenia, reflected in impaired generation of event-related potential (ERP) measures such as auditory mismatch negativity (MMN). MMN is an EEG-derived ERP elicited by deviant stimuli in an auditory oddball paradigm, and it is a robust predictor of psychosis onset in clinical high risk (CHR) cohorts. Herein, we examined auditory MMN in a clinical high risk (CHR) cohort, using a paradigm developed by DC Javitt, and assessed which MMN deviants were abnormal in CHR patients, and the association of MMN with prodromal symptom severity.
METHODS: Participants included fifteen CHR participants and 9 healthy controls (HC), who completed an auditory MMN paradigm with deviants in duration, frequency, intensity, frequency modulation and “change of location”. Positive and negative symptom severity in CHR patients

were assessed using the Structured Interview for Psychosis-Risk Syndromes (SIPS).
RESULTS: In this small study, between-group independent t-tests showed significantly reduced MMN in CHR only for the duration deviant [t(22) =-2.40, p=.03]. Among CHR patients, duration MMN was associated with total positive symptom severity (r=.55, p=.03), whereas frequency modulation MMN was correlated with severity of unusual thought content/delusional ideas (SIPS P1; r=.74, p=.002). Decreased expression of emotion (SIPS N3) was correlated with frequency modulation MMN (r=.58, p=.02), increased pitch MMN (r=.55, p=.03), and decreased intensity MMN (r= .56, p= .03).
CONCLUSIONS: Data collection is ongoing. Our main finding to date is that duration MMN is significantly reduced in CHR patients, in whom it is associated with total positive symptom severity. Exploratory analyses showed that a specific negative symptom, decreased expression of emotion, was associated with a range of deviants, including frequency modulation, frequency and intensity. These findings replicate other studies that identify that duration MMN is among the most replicated biomarkers of psychosis risk.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.12/BB79

Topic: H.03. Schizophrenia

Support: National Institute of Mental Health (R01MH105246)

Title: Investigating the relationship between paracingulate sulcus length and verbal source monitoring in clinical high risk for psychosis individuals

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Abstract: The paracingulate sulcus (PCS) shows considerable morphometrical variability and its absence has been associated with various forms of psychopathology. Reduced PCS length is associated with hallucinations in schizophrenia patients and with misattribution of self- vs other-generated speech in healthy individuals experiencing auditory perceptual disturbances. However, the relationship between PCS length and reality monitoring has not been examined in individuals at clinical high risk for psychosis (CHRp). This study uses a verbal source memory task to measure reality monitoring in CHR individuals with and without a PCS. We hypothesize that those with shorter or absent PCS will have impaired performance on the task compared to those with a present or prominent PCS.

55 CHR individuals were identified using the Structured Interview of Psychosis-risk Symptoms and completed a battery of clinical and cognitive measures. For the Source Memory task, subjects read a list of sentences, half of which must completed and half of which have a response provided. fMRI was acquired during a subsequent recall phase in which the subject indicates the source of each response. MPRAGE T1-weighted structural scans were also acquired and using a standardized protocol, the PCS was identified, traced, and categorized into prominent, present and absent.
Overall, participants had an 88.99% response accuracy (11.4% SD) with no significant differences between self- (88.3%) and other-generated words (89.7%) and no significant differences in reaction time. Analysis between the PCS categories showed similar accuracy rates across categories with no group differences in accuracy or reaction time. Furthermore, we found no significant relationships between task performance, PCS length, IQ or ratings of abnormal perceptual experiences.
These results suggest that individual differences in PCS morphometry may not be significantly related to the development of source monitoring impairments or perceptual abnormalities in CHR individuals. However, individuals' high accuracy on the Source Memory task suggests that the observed results may have been limited by ceiling effects. Further research may benefit from measures more sensitive to disruptions in reality monitoring early in the course of psychosis development.

Disclosures: **A. Lee:** A. Employment/Salary (full or part-time):; Rush University Medical Center. **S. Lokey:** A. Employment/Salary (full or part-time):; Rush University Medical Center. **K. Haut:** A. Employment/Salary (full or part-time):; Rush University Medical Center. **S. Pridgen:** A. Employment/Salary (full or part-time):; Rush University Medical Center. **C.I. Hooker:** A. Employment/Salary (full or part-time):; Rush University Medical Center. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Posit Science.

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.13/BB80

Topic: H.03. Schizophrenia

Support: NIMH Intramural Research Program

Title: Increased functional connectivity of the insula during emotional face recognition in patients with schizophrenia

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Abstract: Introduction Patients with schizophrenia (SZ) struggle with emotional face recognition. Although default mode network hypoconnectivity (Gohari et al., 2017) during facial emotion discrimination as well as altered insular connectivity to the salience network (Pang et al., 2017, Mikolas et al., 2016, Manoliu et al., 2013) in SZ have been reported, functional connectivity of the insula during recognition of faces showing emotion has not been explored in this population. **Methods** Here, we used an independently-derived insula parcellation to test whether SZ patients exhibit altered insular connectivity during recognition of faces showing emotion. 3T BOLD fMRI data were acquired during an emotional face matching task in 208 SZ patients (mean age 31.5+/-9.8, 147 males; 97%+/-7.4 task accuracy) and 766 healthy volunteers ([HVs], mean age 31.0+/-9.2, 322 males; 99%+/-3.1 accuracy). Using a two-cluster insula parcellation independently derived from multimodal neuroimaging data (Kelly et al., 2012), pathophysiological interactions (PPIs) of the anterior and posterior insula with facial emotion viewing were compared between patients and HVs, controlling for age, sex, task accuracy, and reaction time. **Results** Patients exhibited hyperconnectivity of the right anterior insula with the left orbitofrontal cortex, midcingulate cortex, and ventral striatum as well as of the right posterior insula with bilateral amygdalae, bilateral orbitofrontal cortices, left frontal operculum, and left DLPFC ($p<0.05$, FDR-corrected). Functional connectivity of left insula regions did not reach significance after FDR-correction but showed trend-level ($p<0.001$) hyperconnectivity patterns that were similar to findings in the right insula. For all regions, HVs exhibited anticorrelation with the insular seed regions while SZ patients showed positive connectivity with each region ($p's<0.05$, FDR corrected). No regions showed insular hypoconnectivity in SZ. **Conclusion** Here, we show that while matching emotional faces, SZ patients have abnormally increased functional connectivity between the insula and several regions involved in emotion processing. While we controlled for task accuracy, further investigation of whether such insular hyperconnectivity helps or hinders task performance within the SZ population may clarify the meaning of this aberrant connectivity pattern.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.14/BB81

Topic: H.03. Schizophrenia

Support: NIMH Grant R01MH105411

Title: Task-specific disruptions in theta oscillations associated with impaired working memory for temporal order in people with schizophrenia

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Abstract: People with schizophrenia (SZ) have marked deficits in working memory (WM) that contribute to impairments in other cognitive domains and relate to poor functional outcomes. Previous research demonstrated that people with SZ are most impaired at WM tasks that require processing of, and memory for, relationships between items, such as temporal order. The goal of this study was to utilize EEG to examine the impact of SZ on frontal theta oscillations (4-7 Hz) during WM maintenance and its association with deficits in WM for temporal order. EEG data were acquired on 50 people with schizophrenia (SZ) and 61 demographically matched healthy controls (HC) while participants performed two WM tasks. Data were excluded for 7 SZ and 4 HC due to persistent artifacts or below chance performance, leaving a final sample of 43 SZ and 57 HC. On each trial, participants viewed 4 sequential fractal images and, after a 3000 ms delay, a test screen was shown. On “Order” trials they were shown two items from the memory set and they were to select the more recently presented item. On “Item” trials, they were shown one new item and one item from the memory set and asked to select the previously studied item. EEG analyses revealed that oscillatory power in the alpha (9-11 Hz) power was generally reduced in SZ, whereas SZ disruptions in theta (4-7 Hz) power were specific to Order trials. In addition to reduced theta power on Order trials, SZ also showed an altered relationship between theta oscillations and performance on the order task, such that stronger theta band activity predicted higher accuracy in the order task in HC, but not in SZ. These results suggest that reduced theta oscillations and disrupted brain-behavioral relationships during WM maintenance of temporal order are a candidate mechanism for temporal order WM deficits in people with SZ.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.15/BB82

Topic: H.03. Schizophrenia

Title: Subjective language aptitude is linked to neural activity in Broca's area, but not to objective performance during a semantic priming task

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Abstract: Language, including speech and thought, is often affected in mental illnesses. In psychosis, the dimension of language symptoms shows a great variability between patients. A dimensional approach allows to study language as continuum from health to psychosis. Therefore, in the current study, we investigated the heterogeneity of a healthy population during a language task, additionally to a subjective rating of one’s language aptitude. The aim was to analyze the spectrum of inter-individual differences and its association with language-related brain networks, specifically Broca’s area. The observed heterogeneity in the healthy group would enable an extrapolation to clinical end of the spectrum. To this end, 102 healthy adult subjects performed a lexical priming task while measuring brain activity with fMRI. Subjects had to indicate whether a visually presented target word would form the generic term of a previously shown prime word, in terms of its category (e.g. Apple - Fruit) or its relation (e.g. Apple - Pear). To see the difference in language aptitude, we asked the participants to rate on 7-point Likert scale, how they thought their language abilities are. According to the rating they were then grouped into high, mid or low language aptitude groups. Although reaction time (RT) and accuracy showed no significant differences between all three groups, we found differences in brain activation in BA45 among the language aptitude groups. We looked at activation in the Broca areas (BA45, BA44) during preparation (waiting for the target after the indication of task type) and processing (target word processing) phases. We found differences between the groups in BA45 during the preparation and processing phases. The Post hoc analysis revealed that the high group showed significantly greater activation in BA45 compared to the low group, while there was no significant difference between the groups in BA 44. Furthermore, the RT was correlated with activation of BA 45 in the high language aptitude group during the preparation phase, indicating that increased activation in BA45 reflects faster responses in the high language aptitude group. Moreover, for the other two groups correlations with RT were found in BA44.

These results show that, according to subjective evaluation of their own language aptitude, one differently utilizes the language-related brain areas during the language task. These insights into the dimension of language is facilitating upcoming research, that compares these healthy population profiles to the profiles of a population with psychosis.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

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Program #/Poster #: 519.16/BB83

Topic: H.03. Schizophrenia

Title: Posterior striatal dopamine infusion increases striatal and auditory cortical Fos expression to a greater extent in proestrus than in metestrus female rats

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Abstract: Brain mechanisms underlying the complex symptoms of schizophrenia are unknown, but the most supported theory involves excessive dopamine stimulation. For example, all major medications that treat schizophrenia symptoms, such as hallucinations, block D_2-like dopamine receptors in the brain. We have shown that the pattern of cortical activity resulting from a targeted infusion of dopamine into the posterior striatum of male rats resembles the pattern produced in response to auditory stimulation. Our recent studies suggest that females may be more sensitive to dopamine during proestrus. Therefore, we examined the effect of striatal dopamine infusion on Fos expression in female rats across the estrous cycle. We hypothesized that Fos expression would be enhanced by dopamine infusion in females during proestrus/estrus compared to metestrus/diestrus. Adult female Sprague Dawley rats were housed in reverse light-dark conditions (lights on 0900). Stereotaxic surgery was used to place unilateral guide cannulas, and vaginal smears were conducted to determine the estrous stage. Rats then received dopamine (50 nM) or saline vehicle through an infusion cannula targeting the posterior caudatoputamen (CP; AP: -1.80 mm, ML: 4.4 mm, and DV: 5.0 mm) at 0.2 µl/min for 5 min. Immediately thereafter, rats were placed into a sound-attenuated chamber with 75 dB background noise for 90 min. Twenty µm brain sections were collected for immunohistochemistry, and regional Fos labeling density was quantified in striatum and auditory cortex. Dopamine significantly increased Fos labeling in CP during both proestrus/estrus ($p< 0.01$) and metestrus/diestrus ($p < 0.01$) compared to saline infusion. Auditory cortex exhibited dopamine-induced increase of Fos

labeling compared to saline during proestrus/estrus ($p < 0.01$), but not during metestrus/diestrus. Dopamine infusion during proestrus/estrus increased Fos labeling significantly more than during metestrus/diestrus in both CP ($p < 0.01$) and auditory cortex ($p < 0.01$). Thus, dopamine infusion induced Fos labeling in the striatum, probably in direct projection neurons. Dopamine produced significantly greater Fos induction in auditory cortex during proestrus/estrus than during metestrus/diestrus. We conclude that striato-pallido-thalamo-cortical circuits affecting auditory cortex may be more sensitive to dopamine during proestrus/estrus, which could have implications for auditory symptoms in women with schizophrenia during the estrogen phase of the menstrual cycle.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

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Topic: H.03. Schizophrenia

Support: NIH Grant MH116038
NIH Grant MH112189

Title: Neuro-behavioral multivariate markers for personalized patient segmentation, selection and treatment response prediction along the psychosis spectrum

Authors: ***J. JI**[1], M. HELMER[2], J. B. BURT[1], B. ADKINSON[1], A. KOLOBARIC[1], M. FLYNN[1], N. HILL[1], C. H. SCHLEIFER[1], Z. TAMAYO[1], A. SAVIC[4], Y. CHO[1], G. REPOVS[5], J. D. MURRAY[2], A. ANTICEVIC[3];
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Abstract: One of the key challenges in psychiatry is selecting patients for effective treatments. Currently, there is no biologically-grounded framework for psychiatric diagnoses, patient segmentation or predicting a given patient's response to a treatment. While many studies of psychosis-spectrum disorders have found significant differences in behavioral or neural properties at the group level compared to healthy control cohorts, accurate inference and prediction at the single-subject level has remained a barrier for actionable personalized impact. Practically, patients with the same 'binary' DSM diagnosis exhibit a great deal of neural and behavioral heterogeneity. Understanding the mapping between specific symptoms and clinically meaningful neural variation is therefore critical to administering and developing effective individualized treatments.

Here, we build upon our prior work on the Neuro-Behavioral Relationships in Dimensional Geometric Embedding (N-BRIDGE) framework, under which behavioral variation can be mapped to variation in specific neural features in a clinically-informed manner. The neuro-behavioral (N-B) geometry was established using neural (fMRI-derived) and behavioral data from 436 psychosis-spectrum patients and 202 healthy controls. Previously we identified dimensions of behavioral variation in patients and showed that variation along these axes relate to variation in BOLD resting-state measures of global brain connectivity, revealing specific neural systems. These N-B relationships are robust and stable across sites, as well as in k-fold cross-validation, leave-one-out cross-validation, and split-half replication.
Critically, we show here that these behavioral dimensions can be used precisely predict clinically-meaningful neural variation at the individual patient level. Furthermore, we show that these predictions are robust in an independent out-of-sample dataset of patients diagnosed with schizophrenia (N=30) as well as patients with obsessive-compulsive disorder (N=39), a non-psychosis disorder. Lastly, we demonstrate how N-BRIDGE can be used to identify therapeutic targets for personalized patient-specific N-B profiles.
Using N-BRIDGE, we highlight a path for identifying molecular or behavioral targets in a neurobiologically-grounded, data-informed manner. In turn, this path allows for development of therapeutics that are rationally designed around person-specific N-B alterations. We show how multi-variate approaches like N-BRIDGE will be critical for developing rational, targeted, individualized, and maximally effective treatments for mental health symptoms.

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Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.18/BB85

Topic: H.03. Schizophrenia

Support: NIMH PSC-1004-14

Title: Functional connectivity changes in emotion processing network following social cognitive training in individuals with psychosis

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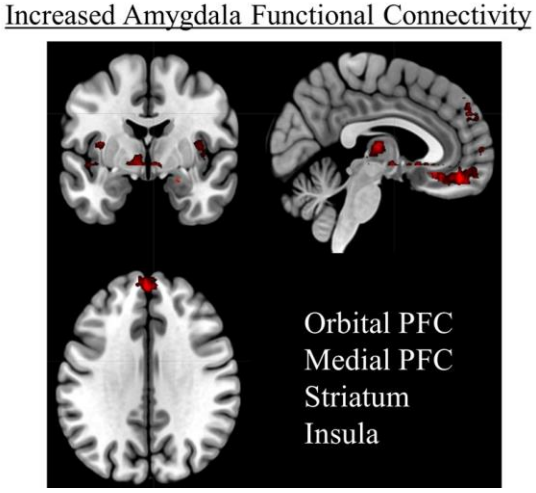
Abstract: Deficits in social cognition play a large role in functional impairments and disability in individuals with schizophrenia and are associated with altered activity in underlying functional networks. Cognitive training on abilities that support social cognition, such as emotion recognition, may improve these deficits. This study assesses changes in social cognitive functional networks following targeted cognitive training in individuals with schizophrenia. 52 individuals with schizophrenia spectrum disorders underwent a clinical evaluation and a functional MRI session prior to and subsequent to completing 40 hours (over ~8 weeks) of either targeted social cognitive training using SocialVille (brainhq.com)(N=27) or a computer game control condition (N=25). Resting state fMRI was acquired as well as fMRI during performance of an emotion recognition task and changes in emotion processing network activation and functional connectivity was evaluated. Individuals who received social cognitive training showed improved accuracy of emotion recognition compared to those in the control condition ($t(50)=2.16$, $p=.036$). Training was associated with altered activity within the emotion processing network, including the amygdala and superior temporal sulcus (STS). In addition, altered STS-medial prefrontal connectivity, amydala-orbitofrontal connectivity and amygdala-insula connectivity was found. These results suggest that targeted social cognitive training may be effective in altering functional network connectivity in networks associated with deficits in individuals with psychosis and may be a useful tool for intervention in individuals with psychotic disorders.



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Poster

519. Clinical and Biomarker Research in Schizophrenia

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Program #/Poster #: 519.19/CC1

Topic: H.03. Schizophrenia

Support: MH077862
MH077852
MH078113
MH077945
MH077851

Title: Caudate connectivity and antipsychotic medication dose in psychosis patients

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Abstract: Background:
Antipsychotic medication influences resting brain network function as measured in fMRI studies. However, the influence of antipsychotic medication on brain function often is not examined directly, especially in studies of subjects taking different antipsychotic medications. Instead, antipsychotic medication is treated as an unexamined covariate, quantified via chlorpromazine dose equivalence estimates (CPZ). The current study aims to identify brain function effects associated with this common medication quantification approach. We focused our assessment on connectivity of the caudate; given this structure is a site of direct antipsychotic medication effect associated with efficacy at reducing psychosis symptoms.
Method:
We assessed connectivity in resting state functional MRI data collected from a subsample of participants of the multisite Bipolar Schizophrenia Network on Intermediate Phenotypes (BSNIP1) study. The subsample was selected for having adequate antipsychotic dose information available for CPZ calculation and for having fMRI data that passed stringent quality assessment criteria. The final sample included those diagnosed with schizophrenia (n = 82), schizoaffective disorder (n = 77), or bipolar disorder with psychosis (n = 91), and healthy controls (n = 173). Using the CONN toolbox, a bilateral caudate seed was used to generate connectivity maps for each subject. These connectivity maps were used in a whole brain regression analyses with CPZ, covarying for age, sex, and study site.

Results:
Higher antipsychotic dose was associated with greater connectivity of the caudate to the precuneus (cluster size = 286 mm^3, p= 0.0002) voxel threshold criteria of p<.001 uncorrected, and a cluster threshold of p <0.05 FWE.

Discussion:
We found that higher antipsychotic medication doses associated with greater connectivity between caudate and precuneus. The precuneus is a node of the default mode network (DMN), which has been reported to be altered in schizophrenia and other psychotic disorders. Specifically, greater connectivity has been found between DMN nodes including precuneus in schizophrenia compared to controls and to first degree relatives. Our findings suggest that such neural system alterations may be equally due to antipsychotic medication as well as illness effects. Future work will include assessments of alternative CPZ estimates and other metrics of resting state fMRI.

Disclosures: E. Herms: None. **J. Wren-Jarvis:** None. **J. Bishop:** None. **V. Okuneye:** None. **M. Keshavan:** None. **C.A. Tamminga:** None. **G. Pearlson:** None. **J. Sweeney:** None. **S. Keedy:** None.

Poster

519. Clinical and Biomarker Research in Schizophrenia

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 519.20/CC2

Topic: H.03. Schizophrenia

Support: NARSAD Young Investigator Grant
McLean Hospital Lorenz-Pope Fellowship
Broad Institute of Harvard and MIT Stanley Center Psychiatric Genetics and Neuroscience Fellowship

Title: Increased entropy of microstate sequences in first episode psychosis

Authors: *M. MURPHY, D. ÖNGÜR;
Harvard Med. Sch., Boston, MA

Abstract: Psychosis is commonly thought to be related to dysconnectivity between regions of the brain. We used microstate analysis to compress resting state high-density (hd-EEG) data from patients with first-episode psychosis and healthy controls into sequences of characteristic scalp topographies. We found that patients and controls produced similar sets of four microstates that agree with a canonical set of microstates widely reported in the literature. We found that microstate A was decreased in patients compared to controls. We then used sample entropy to calculate the complexity of the microstate sequences across a range of template lengths. For a

given template length *m*, the sample entropy is a measure of how likely two identical sequences of length will not be identical at length *m* + 1. We found that in controls, sample entropy decreased as template length increased, suggesting that control resting state data is self-similar. In patients, we found that sample entropy did not decrease. We show that this finding is unrelated to the length of the data or the topography of the microstates. We show that entropy is elevated in unmedicated patients and decreases with medication dosage. We also identify patterns of transitions between microstates that are overrepresented in control data and in patient data. Given previous work that has linked microstates with resting state networks, our findings suggest that, in addition to any disruption within brain networks, transitions between networks are abnormally chaotic in patients with first-episode psychosis.

Disclosures: **M. Murphy:** None. **D. Öngür:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.01/CC3

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NIH DP2
NCSOFT
Picower Institute
Packard Fellowship

Title: Non-parametric hyperdimensional analysis of multiscale phenotypic factors in intact cerebral organoids

Authors: ***J. SWANEY**[1], A. ALBANESE[2], D. YUN[2], N. EVANS[3], L. KAMENTSKY[4], M. KIM[4], C. SOHN[4], J. ANTONUCCI-JOHNSON[4], V. PHAM[4], C. DELEPINE[5], M. SUR[5], L. GEHRKE[4], K. CHUNG[5];
[1]Dept. of Chem. Engin., [2]Inst. for Med. Engin. and Sci., [3]Picower Inst. for Learning and Memory, [5]Dept. of Brain and Cognitive Sci., [4]MIT, Cambridge, MA

Abstract: Cerebral organoids are the most complex *in vitro* model of the developing human brain to date. At the single-cell level, cerebral organoids contain diverse cell populations with distinct expression patterns, and at the tissue level, cytoarchitectures observed during human cortical development begin to emerge. However, current techniques used to characterize cerebral organoids do not scale across these different length scales. Here, we present a tissue processing pipeline for whole-organoid antibody labeling and imaging as well as a computational framework for extracting and analyzing multiscale phenotypic factors from these images. SHIELD tissue processing preserves protein epitopes, mRNA, and endogenous fluorescence in

intact cerebral organoids and produces optically transparent samples that can be imaged using light-sheet microscopy. The computational framework segments all nuclei using a curvature-based seeded watershed algorithm and classifies cell types based on the mean fluorescence intensity of each cell type marker. The spatial proximity to progenitor cells (SOX2) and post-mitotic neurons (TBR1) revealed four distinct cellular niches within cerebral organoids cultured for 35 days. A clustering analysis of radial cell profiles identified five types of cortical cytoarchitectures corresponding to different layering patterns of progenitor cells and post-mitotic neurons. By concatenating descriptors of single-cells, cortical cytoarchitectures, and whole-organoid morphology, a hyperdimensional feature vector of multiscale phenotypic factors was constructed for each organoid. Correlation analysis between multiscale phenotypic factors quantified the interscale relationships between cerebral organoids cultured for 35 and 60 days. Permutation testing revealed differences in phenotypic factors corresponding to deficits in cortical development in cerebral organoid models of Zika virus and Rett syndrome. These results demonstrate how phenotypic factors observed from the single-cell level to the tissue level can be integrated into a single, unbiased analysis of intact cerebral organoids.

Disclosures: **J. Swaney:** None. **A. Albanese:** None. **D. Yun:** None. **N. Evans:** None. **L. Kamentsky:** None. **M. Kim:** None. **C. Sohn:** None. **J. Antonucci-Johnson:** None. **V. Pham:** None. **C. Delepine:** None. **M. Sur:** None. **L. Gehrke:** None. **K. Chung:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.02/CC4

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: RIKEN CBS (to ST)
HHMI (to ST)
JBP Foundation (to ST)
Burroughs Wellcome Fund Career Awards (to KC)
Searle Scholars Program (to KC)
Packard award in Science and Engineering (to KC)
NARSAD Young Investigator Award (to KC)

Title: An engram index permits brain-wide mapping of a specific memory

Authors: D. S. ROY[1], ***Y.-G. PARK**[1], S. K. OGAWA[1], J. CHO[1], H. CHOI[1], J. MARTIN[1], K. CHUNG[2,1], S. TONEGAWA[1,2];
[1]The Picower Inst. for Learning and Memory, [2]Brain and Cognitive Sci., MIT, Cambridge, MA

Abstract: Neuronal ensembles that hold specific memory information (memory engrams) have been identified in the hippocampus, amygdala, and multiple cortical areas. It has been suggested that the engram for a specific memory is distributed among multiple brain regions that are functionally connected. Here, we generated a brain-wide putative engram cell ensemble map of 409 regions in contextual fear memory by applying activity-dependent cell labeling, optogenetics, and SHIELD-based tissue clearing. To circumvent the laborious optogenetic demonstration of engram cells, we devised an "engram index" based on the notion that memory engram cells are activated during learning and reactivated during recall, and applied it to rank-order the list of c-Fos$^+$ neuronal ensembles. We then subjected the high rankers to the established optogenetic procedures, which confirmed the previously demonstrated engram cell ensembles as well as revealed new engrams in thalamic nuclei. Crucially, optogenetic reactivation of not all c-Fos$^+$ neuronal ensembles resulted in memory retrieval, suggesting that these ensembles do not carry engrams for this memory. We also show that the engram cell ensembles reactivated by natural recall cues match well with those reactivated by optogenetics. Further, optogenetic reactivation of CA1 or BLA engram cells caused a pattern of increased activation of engram cell ensembles (both demonstrated and putative) in multiple brain regions, indicating functional connectivity of these ensembles. Finally, simultaneous chemogenetic reactivation of multiple engram cell ensembles, which mimics better the natural process of memory recall, resulted in a greater level of recall than a single engram ensemble reactivation. Overall, our study supports the hypothesis that a memory is stored in a specific pathway of multiple engram cell ensembles.

Disclosures: D.S. Roy: None. **Y. Park:** None. **S.K. Ogawa:** None. **J. Cho:** None. **H. Choi:** None. **J. Martin:** None. **K. Chung:** None. **S. Tonegawa:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.03/CC5

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Burroughs Wellcome Fund Career Awards at the Scientific Interface
the Searle Scholars Program
Packard award in Science and Engineering
NARSAD Young Investigator Award
McKnight Foundation Technology Award
JPB Foundation (PIIF and PNDRF)
NCSOFT Cultural Foundation

Title: Multiplexed organ-wide mapping of biomolecules using oligonucleotide labeling

Authors: *C. H. SOHN[1,2], Y. TIAN[3,2], M. E. KIM[1,2], N. P. TOWNSEND HASS[3,2], L. DELORENZO[1,2], K. CHUNG[1,2,3,4];
[1]Inst. of Med. Engin. and Sci., [2]Picower Inst. of Learning and Memory, [3]Chem. Engin., MIT, Cambridge, MA; [4]Broad Inst. of MIT and Harvard, Cambridge, MA

Abstract: Investigating biomolecules at cellular levels within the spatial context is key for understanding the brain function and dysfunction. Immuno-fluorescence (IF) staining and fluorescence *in situ* hybridization (FISH) of multiple targets are invaluable tools for cell type mapping but multiplexing has been challenging primarily due to the spectral overlap of fluorescent dyes and the limited antibody host variety. In addition, the methods used for highly multiplexed mRNA mapping is inapplicable to IF-based protein mapping. Finally, organ-scale samples often require several orders of magnitude more time for multi-round labeling, imaging, and registration, rendering the multiplexing strategy employed for thin single-cell layer samples nearly impractical for thick intact samples. Therefore, we sought a new approach to enable highly multiplexed three-dimensional volumetric staining and imaging of large-scale brain tissues. To take advantage of the barcoding strategy, we conjugated antibodies with short single-strand DNA oligonucleotides. The resulting oligo conjugates can be employed for simultaneous immunostaining of multiple targets without the host overlap issue. We optimized the antibody-oligonucleotide conjugation chemistry to be substantially low cost in comparison with expensive commercial kits, while allowing multiple oligo labeling without perturbation of antigen binding sites. The labeling method presented here is applicable to any antibody hosts and is scalable up to several mg quantities. In addition, we adopted multiplexed signal amplification methods with photostable dyes to minimize photobleaching and to enable ultrafast imaging of large-scale tissue using light-sheet microscopy. Overall, the tool kits presented here will allow high-throughput multiplexed mapping of biomolecules in organ-scale samples.

Disclosures: C.H. Sohn: None. **Y. Tian:** None. **M.E. Kim:** None. **N.P. Townsend Hass:** None. **L. DeLorenzo:** None. **K. Chung:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.04/DP13/CC6

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Burroughs Wellcome Fund Career Awards at the Scientific Interface
the Searle Scholars Program
Packard award in Science and Engineering

NARSAD Young Investigator Award
McKnight Foundation Technology Award
JPB Foundation (PIIF and PNDRF)
NCSOFT Cultural Foundation

Title: Ultrafast brain-wide immunostaining for scalable single-cell-resolution proteomic phenotyping

Authors: *D. YUN[1,2], Y.-G. PARK[1,2], J. H. CHO[3], L. KAMENTSKY[1], N. EVANS[1], K. XIE[1], A. ALBANESE[1], J. SWANEY[3], Y. TIAN[3], C. SOHN[1], W. GUAN[3], G. DRUMMOND[2], H. CHOI[1], T. KU[1], Q. ZHANG[2,4], H.-Y. JUNG[1], L. RUELAS[3], G. FENG[2,4], K. CHUNG[1,2,5,3,6]; [1]Inst. for Med. Engin. and Sci., [2]Dept. of Brain and Cognitive Sci., [3]Dept. of Chem. Engin., [4]McGovern Inst. for Brain Res., [5]Picower Inst. for Leaning and Memory, MIT, Cambridge, MA; [6]Broad Inst. of Harvard Univ. and MIT, Cambridge, MA

Abstract: Advances in intact tissue clearing and imaging modalities are enabling rapid visualization and 3D phenotyping of large tissues; however, molecular labeling of intact tissue remains laborious and low throughput. Here, we introduce an ultrafast method, eFLASH (electrophoretically driven Fast Labeling using Affinity Sweeping in Hydrogel), that permits organ-scale immunolabeling on the same time scale as conventional immunohistochemistry on thin tissue sections. eFLASH utilizes chemical strategy to modulate labeling reactions in the context of ultrafast probe transport mediated by Stochastic electrotransport (Kim, PNAS, 2015). With a universal 1-day protocol, eFLASH allows uniform labeling of mouse organ-scale tissues with a wide-range of antibodies, generating high-quality samples suitable for automated quantitative analysis of various proteins indicating cell types or functional activity. Universal nature of eFLASH allows labeling of disparate tissue types using the same protocol including models with restricted access to genetic labeling tools, and we have demonstrated its application on mouse brains, marmoset brain block, and human iPSC-derived cerebral organoid by achieving multi-probe labeling in each type. Finally, eFLASH leverages robust preservation of biomarkers and tissue architecture provided by SHIELD (Park, NBT, 2019), which allows repeated immunolabeling of rare or precious samples. We envision that eFLASH will spur multidimensional and holistic phenotyping of emerging animal models and disease models to help assess their functions and dysfunctions.

Disclosures: **D. Yun:** None. **Y. Park:** None. **J.H. Cho:** None. **L. Kamentsky:** None. **N. Evans:** None. **K. Xie:** None. **A. Albanese:** None. **J. Swaney:** None. **Y. Tian:** None. **C. Sohn:** None. **W. Guan:** None. **G. Drummond:** None. **H. Choi:** None. **T. Ku:** None. **Q. Zhang:** None. **H. Jung:** None. **L. Ruelas:** None. **G. Feng:** None. **K. Chung:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.05/CC7

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Burroughs Wellcome Fund Career Awards at the Scientific Interface
Searle Scholars Program
Packard award in Science and Engineering
NARSAD Young Investigator Award
McKnight Foundation Technology Award
JPB Foundation (PIIF and PNDRF)
NCSOFT Cultural Foundation

Title: Mechanical interlocking of biomolecules *in situ* preserves tissue architecture and integrity of biomolecules

Authors: *Y. TIAN[1], J. T. MARTIN[2], X. JIN[8,3], D. J. IRVINE[4,2,9,5,10], K. CHUNG[1,8,3,6,7]; [1]Chem. Engin., [2]Koch Inst. for Integrative Cancer Res., [3]Inst. for Med. Engin. and Sci., [4]Biol. Engin., [5]Material Sci. and Engin., [6]Picower Inst. for Learning and Memory, [7]Brain and Cognitive Sci., MIT, Cambridge, MA; [8]Broad Inst. of Harvard Univ. and MIT, Cambridge, MA; [9]Ragon Inst. of Massachusetts Gen. Hospital, Massachusetts Inst. of Technol. and Harvard Univ., Cambridge, MA; [10]Howard Hughes Med. Inst., Chevy Chase, MD

Abstract: Interrogating the spatial distribution and function of biomolecules in multicellular organisms is crucial for a wide range of biomedical research. However, chemical processes needed to preserve the physical structure of tissues often cause loss of biomolecular function. Most existing tissue preservation strategies use chemical fixatives to preserve spatial organization of biomolecules, but chemical modification in this process often sacrifices the integrity and activity of biomolecules and their dynamic interactions. Here we introduce a method for permanent mechanical interlocking of biomolecules across multiple scales, from the nanoscale of single biomolecules to the organ scale, without chemical damage. The method relies on the trapping and interlocking effect of polymer chains rather than the intense chemical crosslinking and modification mediated by fixatives in conventional tissue processing technologies. We confirm that the spatial distribution and the antigenicity of biomolecules are well preserved by mechanical interlocking of hydrogel. We show that the functionality of biomolecules is less affected due to the lack of aggressive fixation chemistry, and multiple functional assays can be easily applied after imaging. The new technology is applicable to a wide range of contents, from free proteins, nucleic acids, cells, to biological tissues, and ensures a good preservation of biomolecules and their functions. It has been applied to brain tissues and

lymph node tissues to study various questions that could not be addressed with conventional chemical fixation-based methods.

Disclosures: **Y. Tian:** None. **J.T. Martin:** None. **X. Jin:** None. **D.J. Irvine:** None. **K. Chung:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.06/CC8

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Burroughs Wellcome Fund Career Awards
Searle Scholars Program
Packard Award in Science and Engineering
NARSAD Young Investigator Award
McKnight Foundation Technology Award
JDP Foundation
NCSOFT Cultural Foundation

Title: SHIELD protocols for scalable tissue protection and imaging

Authors: *K. XIE[1,2], S. CHOI[3], H. AHN[5], Y.-G. PARK[1,2], C. SOHN[1,2], D. YUN[1,2], N. EVANS[1,2], E. NICHOLS[6], K. SAIJO[6], K. CHUNG[4,2,3,1,7];
[1]Inst. for Med. Engin. and Sci., [2]Picower Inst. for Learning and Memory, [3]Dept. of Chem. Engin., [4]Dept. of Brain and Cognitive Sci., MIT, Cambridge, MA; [5]Yonsei-IBS Inst., Yonsei Univ., Seoul, Korea, Republic of; [6]Dept. of Mol. and Cell Biol., Univ. of California Berkeley, Berkeley, CA; [7]Broad Inst. of Harvard Univ. and MIT, Cambridge, MA

Abstract: Advances in tissue processing and preservation techniques have given rise to phenotyping capacity on a previously unprecedented scale. However, the scalability of such methods and the degree of molecular preservation have remained a challenge. Using SHIELD (**S**tabilization to **H**arsh conditions via **I**ntramolecular **E**poxide **L**inkages to prevent **D**egradation; Park, Nature Biotechnology, 2019), we have previously demonstrated that it is possible to preserve protein fluorescence, nucleic acids, antigenicity, and tissue architecture through the fixation of biological samples with a versatile polyepoxide crosslinker. SHIELD expands upon conventional fixative-based tissue preservation by using a five-arm polyepoxide crosslinker, P3PE. The macromolecules are uniformly dispersed throughout the tissue and simultaneously crosslinked into a tight network via a series of simple buffer changes. The preserved tissue can then be subjected to a variety of treatments, including whole-organ clearing, volumetric immunostaining, and high-throughput volumetric imaging. We show here that the SHIELD

protocol is easily scalable and has been successfully implemented in the analysis of embryonic and adult mouse brains, adult mouse organs, adult human brains, and cerebral organoids. Moreover, SHIELD can be combined with downstream processing methods such as MAP (Ku, Nature Biotechnology, 2016) and eFLASH to enable rapid and holistic interrogation of large-scale biological systems. We anticipate that SHIELD protocols will allow integrated structural and molecular phenotyping of a wide range of biological tissues.

Disclosures: **K. Xie:** None. **S. Choi:** None. **H. Ahn:** None. **Y. Park:** None. **C. Sohn:** None. **D. Yun:** None. **N. Evans:** None. **E. Nichols:** None. **K. Saijo:** None. **K. Chung:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.07/CC9

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NSF Graduate Research Fellowship Program
Burroughs Wellcome Fund Career Awards at the Scientific Interface
Searle Scholars Program
Packard Award in Science and Engineering
NARSAD Young Investigator Award
McKnight Foundation Technology Award
PB Foundation (PIIF and PNDRF)

Title: A scalable pipeline for comprehensive single-cell resolution mapping of the human brain

Authors: *W. GUAN[1], T. KU[2,3], N. EVANS[2,3], Y.-G. PARK[2,3], C. SOHN[2,3], D. YUN[2,3], J. WANG[5], S.-C. CHEN[5], M. FROSCH[6], K. CHUNG[1,2,3,4,7];
[1]Chem. Engin., [2]Picower Inst. for Learning and Memory, [3]Inst. for Med. Engin. and Sci., [4]Brain and Cognitive Sci., MIT, Cambridge, MA; [5]Mechanical and Automation Engin., Chinese Univ. of Hong Kong, Shatin, Hong Kong; [6]C.S. Kubik Lab. for Neuropathology, Massachusetts Gen. Hosp. and Harvard Med. Sch., Boston, MA; [7]Broad Inst. of Harvard Univ. and MIT, Cambridge, MA

Abstract: Integrated, multi-scale mapping of the human brain is one of the most sought-after challenges in neuroscience. Due to the brain's size and complexity, state-of-the-art technologies for human brain interrogation must sacrifice either resolution or scalability -- low resolution 3D whole brain visualization (e.g. MRI) vs. molecular resolution nanometer-scale visualization (EM). Histology-based pipelines have also previously been implemented for cellular resolution visualization; however, these require many error-prone processing steps -- such as sectioning the brain into thousands of thin slices -- that also do not preserve 3D connectivity information.

Because of these current limitations, we aimed to develop a novel thick tissue processing, fluorescent labeling, and imaging pipeline that is reliable, able to preserve morphological integrity, and scalable to human brain length scales. Using custom-developed vibratoming, SHIELD-ELAST tissue-hydrogel transformation and clearing, kinetic-modulated immunolabeling, and high resolution selective plane illumination microscopy (SPIM) pipeline, we show that single neuronal axons can be manually traced within 3mm-thick coronal human brain hemisphere blocks. We are able to fix, clear, stain, and image each tissue slab with minimal tissue damage and deformation, high reproducibility, and sufficient image quality for manual long-range tracing of sparse neuronal fibers, demonstrating that this pipeline is scalable to a whole human brain, which would require processing 30-40 coronal slabs of this size. This proof of concept study suggests that single cell resolution mapping on the global human brain scale is possible and could facilitate the development of comprehensive human brain atlases in the future.

Disclosures: **W. Guan:** None. **T. Ku:** None. **N. Evans:** None. **Y. Park:** None. **C. Sohn:** None. **D. Yun:** None. **J. Wang:** None. **S. Chen:** None. **M. Frosch:** None. **K. Chung:** A. Employment/Salary (full or part-time):; LifeCanvas Technologies.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.08/CC10

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: Burroughs Wellcome Fund Career Awards at the Scientific Interface
The Searle Scholars Program
Packard award in Science and Engineering
NARSAD Young Investigator Award
McKnight Foundation Technology Award
JPB Foundation (PIIF and PNDRF)
NCSOFT Cultural Foundation

Title: Scalable cell phenotyping framework for microglial cells

Authors: ***M. E. KIM**[1,2], G. DRUMMOND[2], E. NICHOLS[5], N. B. EVANS[1], Y.-G. PARK[1], N. DINAPOLI[1], D. YUN[1,2], K. XIE[1], J. SWANEY[3], K. SAIJO[5], K. CHUNG[2,3,1,4];
[1]Inst. for Med. Engin. and Sci., [2]Dept. of Brain and Cognitive Sci., [3]Dept. of Chem. Engin., [4]Picower Inst. for Learning and Memory, MIT, Cambridge, MA; [5]Dept. of Mol. Cell Biol., Univ. of California Berkeley, Berkeley, CA

Abstract: Microglia play numerous important roles during the development and aging of the central nervous system (CNS). In response to changes in their surrounding micro-environment, microglia represent an impressive level of functional and morphological plasticity (AyoubAlbert E., 2003) (LawsonL.J., 1990) (LoaneDavid, 2016) (HutchinsKenneth, 1990). Therefore, characterizing their brain-wide organization and functional heterogeneity has become essential to understand the role of microglia in brain function and dysfunction. Yet, most currently available methods are either applied to limited regions or thin slices focused on specific questions (e.g. morphology profiles after neuroinflammation) (StenceNick, 2001), (Fernández-ArjonaMDM, 2017), or require manual analysis that is often biased, inaccurate, and extremely laborious, hence less scalable to broader regions (SwinnenNina, 2012). Here, we propose a scalable and fully automated cell phenotyping framework (S-CPF) that enables fast and comprehensive analysis of both spatial and morphological characteristics of microglia in 3D datasets acquired using SHEILD (ParkYoung-Gyun, 2018), eFLASH, and SPIM imaging. S-CPF achieves state-of-the-art accuracy and scalability in morphology prediction, allowing full analysis of microglia in an entire mouse brain within hours. Brain-wide analyses of microglial cell distribution and characterization of their morphology (e.g., ramified, amoeboid) in mouse brains at different developmental stages validate our framework and prove the high scalability and accuracy. We envision that S-CPF will enable scalable brain-wide phenotyping of microglia for a broad range of research.

Disclosures: M.E. Kim: None. **G. Drummond:** None. **E. Nichols:** None. **N.B. Evans:** None. **Y. Park:** None. **N. DiNapoli:** None. **D. Yun:** None. **K. Xie:** None. **J. Swaney:** None. **K. Saijo:** None. **K. Chung:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.09/CC11

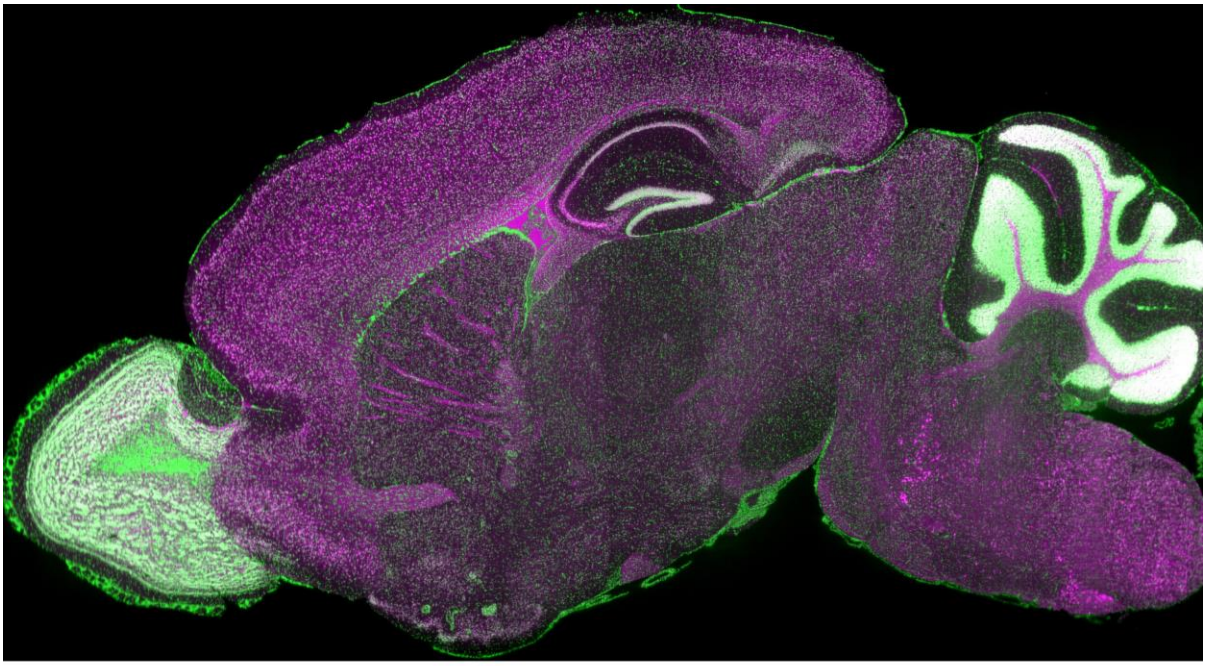
Topic: I.02. Systems Biology and Bioinformatics

Support: WPI-IRCN program
AMED Brain/MINDS
AMED-CREST
AMED the Basic Science and Platform Technology Program for Innovative Biological Medicine
Grants-in-Aid for Scientific Research (S) (18H05270)
Grants-in-Aid from the Takeda Science Foundation

Title: CUBIC fine-vision: A whole-brain cell classification by isometric three-dimensional imaging and analysis

Authors: *M. KURODA[1], T. MANO[2,1], C. SHIMIZU[4], E. A. SUSAKI[3,4,5], H. R. UEDA[3,1,4]; [1]Intl. Res. Ctr. for Neurointelligence (WPI-IRCN), [2]Dept. of Information Physics and Computing, Grad. Sch. of Information Sci. and Technol., [3]Dept. of Systems Pharmacology, Grad. Sch. of Med., The Univ. of Tokyo, Tokyo, Japan; [4]Lab. For Synthetic Biol., RIKEN Ctr. for Biosystems Dynamics Res., Osaka, Japan; [5]JST-PRESTO, Saitama, Japan

Abstract: Recent development of tissue clearing techniques have promised for researchers to visualize deep inside the nervous system. Light-sheet fluorescence microscopy (LSFM) is now a common method to explore a volumetric sample by less-invasive optical slicing. However, there have been few LSFM systems which cover a wide area of imaging with sufficient optical resolution (i.e. a whole brain with subcellular resolution). Thus, we designed a new LSFM system with spatially-uniform thin light-sheet illumination which provides a three-dimensionally isotropic resolution and covers a wide area of visualization; we visualized subcellular structures across entire area of mammalian brains and bodies. Isometric voxel data enable us to analyze the cell architecture based on the three-dimensional morphology regardless of illumination and imaging axis. Also, combined with a whole-brain immunostaining technique (CUBIC-HistoVIsion), each cell can be characterized by cell types and functions in nervous system. Finally, with those dataset, we renewed a point-based mouse brain atlas (CUBIC-Atlas) with annotations and classifications in addition to the position of cells.



Virtual sagittal section of a whole mouse brain reconstructed with horizontal optical slices.
The images were captured by a macroscopic LSFM with isotropic resolution (6.5 μm/voxel).
Neurons (magenta) and cell nuclei (green) are labeled by CUBIC-HistoVIsion.

Disclosures: **M. Kuroda:** None. **T. Mano:** None. **C. Shimizu:** None. **E.A. Susaki:** None. **H.R. Ueda:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.10/CC12

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Support: JST ERATO (JPMJER1801),
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The Human Frontier Science Program (RGP0019/2016),
AMED-CREST
AMED Brain/MINDS
AMED the Basic Science and Platform Technology Program for Innovative Biological Medicine

Title: SeeNet: Hybrid hydrogel and tissue clearing for molecular and structural characterization of cerebral vasculature

Authors: *T. MIYAWAKI[1,2,4,5], E. A. SUSAKI[2,4,6], S. YAMAGUCHI[7,8], H. R. UEDA[2,3,4], Y. IKEGAYA[1,9];
[1]Grad. Sch. of Pharmaceut. Sci., [2]Dept. of Systems Pharmacology, Grad. Sch. of Med., [3]Intl. Res. Ctr. for Neurointelligence (WPI-IRCN), UTIAS, The Univ. of Tokyo, Tokyo, Japan; [4]Lab. for Synthetic Biol., RIKEN Ctr. for Biosystems Dynamics Res., Osaka, Japan; [5]Japan Society for the Promotion of Sci. (JSPS), Tokyo, Japan; [6]PRESTO, Japan Sci. and Technol. Agency (JST), Saitama, Japan; [7]Dept. of Morphological Neuroscience, Grad. Sch. of Med., [8]Ctr. for Highly Advanced Integration of Nano and Life Sci., Gifu Univ., Gifu, Japan; [9]Ctr. for Information and Neural Networks, Natl. Inst. of Information and Communications Technol., Osaka, Japan

Abstract: Cerebral vasculature is a 3D traffic network with blood-brain barrier, a molecularly heterogeneous interface regulating the flow of substances between blood and brain parenchyma. Although structural and molecular analyses of cerebral vasculature are promising for providing fundamental insights into cerebral circulation and cerebrovascular diseases, few studies have captured detailed structural information of molecularly identified vascular networks, due to technical limitations. Here, we introduce SeeNet, a method for near-complete three-dimensional visualization of intact cerebral vascular networks with high signal-to-noise ratios, compatible with molecular phenotyping. SeeNet employs perfusion of a novel multifunctional crosslinker, vascular casting by temperature-controlled polymerization of hybrid hydrogels, and a tissue clearing technique optimized for observation of vascular connectivity. SeeNet was capable of whole-brain visualization of molecularly characterized cerebral vasculatures at the single microvessel level. Moreover, SeeNet revealed a hitherto unidentified vascular pathway. This

technology will routinize large scale 3D tracing of molecularly characterized cerebral vasculature, and will facilitate the future investigation of cerebral circulation under health and disease.

Disclosures: T. Miyawaki: None. **E.A. Susaki:** None. **S. Yamaguchi:** None. **H.R. Ueda:** None. **Y. Ikegaya:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.11/CC13

Topic: I.02. Systems Biology and Bioinformatics

Support: AMED-CREST
AMED Brain/MINDS
AMED the Basic Science and Platform Technology Program for Innovative Biological Medicine
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WPI-IRCN program
Grants-in-Aid from the Takeda Science Foundation
AMED Brain/MINDS (JP19dm0207057)

Title: Advanced CUBIC pipeline in whole-organ cell profiling for biomedical research

Authors: *T. T. MITANI[1], K. MATSUMOTO[1], S. A. HORIGUCHI[1], J. KANESHIRO[1], T. C. MURAKAMI[2], T. MANO[2], H. FUJISHIMA[1], A. KONNO[3], H. HIRAI[3], H. R. UEDA[1,2]; [1]RIKEN Ctr. for Biosystems Dynamics Res., Osaka, Japan; [2]The Univ. of Tokyo, Tokyo, Japan; [3]Gunma Univ., Maebashi, Japan

Abstract: Whole-organ cell profiling pipeline coupled with CUBIC technologies is getting to be an effective tool to obtain comprehensive cell information throughout the organ. Recently, we reported a single-cell-resolution whole-brain atlas (CUBIC-Atlas), which was novel scalable and sharable format among research community for handling the whole-organ data by a point cloud. However, the positions of all detected cells in an organ had to be extracted from a large image data to compact the data size, and therefore the throughput of data collection and analysis remain a severe bottleneck for biomedical applications handling numerous samples. To overcome the obstacle, we developed a high-speed volumetric imaging system together with a high-speed cell detection algorithm for practical use. The stable and efficient imaging methods including adaptive focusing were integrated into a custom-built light-sheet fluorescence microscopy. The acquisition time was shortened to within a few hours per mouse whole organ. For example, using a ten-fold expanded adult mouse whole-brain sample, the throughput of 50 ms of exposure time

was measured as 0.56 TB/h and total data size was 6.3 TB using 10x objective lens with novel imaging system, comparing with 0.15 TB/h and 14 TB with previous imaging scheme (Murakami et al., 2018). Acquisition time per brain also became 8.5 times faster than the previous report. To analyze the large-scale imaging data in a rapid manner, we also developed a cell detection algorithm based on three-dimensional Hessian-based Difference of Gaussian and a highly parallelization of multiple CPUs and GPUs. Our cell-detection algorithm worked at 1 hour/TB and had over 90% F-scores of nuclear stained cell detection throughout the brain. Using a brain transduced with AAV-PHP.eB (NSE-H2B-mCherry) counterstained by nuclear stain dye, we demonstrated the usability of the developed imaging-analysis pipeline by quantification of mCherry positive cell number in each anatomical region and the ratio of positive cells in each 80 μm voxel. These results show that the cortex and hippocampus showed higher positive ratio than other areas. Thus, the pipeline provides a novel platform for the high-speed organ-scale analysis of cells and will promote next-generation biomedical research targeting a large number of samples in a feasible timescale.

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Poster

520. Molecular Structural Imaging

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Topic: I.02. Systems Biology and Bioinformatics

Support: JST PRESTO JPMJPR15F4
KAKENHI Grant 15H05650, 17H06328, 18K19419, 18H05270 and 19H03413
AMED-CREST
AMED Brain/MINDS
AMED the Basic Science and Platform Technology Program for Innovative Biological Medicine
Grants-in-Aid from the Takeda Science Foundation
WPI-IRCN program

Title: A versatile protocol for three-dimensional whole-organ/body staining and imaging with single-cell resolution based on electrolyte-gel properties of biological tissue

Authors: ***E. SUSAKI**[1,3,4], C. SHIMIZU[4], A. KUNO[7], K. TAINAKA[8], X. LI[10], K. NISHI[10], H. ONO[1], K. L. ODE[1], Y. SAEKI[11], K. MIYAMICHI[12,13], K. ISA[14], C. YOKOYAMA[5], H. KITAURA[9], M. IKEMURA[2], T. USHIKU[2], Y. SHIMIZU[6], T. SAITO[15], T. C. SAIDO[15], M. FUKAYAMA[2], H. ONOE[16], K. TOUHARA[12,13,17], T. ISA[14], A. KAKITA[9], M. SHIBAYAMA[10],

H. R. UEDA[1,4,17];
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Abstract: The recent development of various tissue clearing and three-dimensional (3D) imaging methods, including our CUBIC pipeline [1-3], allowed the comprehensive observation of whole organ/body with cellular resolution or more. However, in the long history of histology, whole-organ/body 3D staining and imaging have been still challenging due to the difficulty of adequate penetration of stains and antibodies. Even a small dye occasionally exhibits the resistance to penetration, implying the existence of a complex physicochemical environment in the staining system. Here, we report a universal whole-organ/body staining and imaging protocol named CUBIC-HistoVIsion. To dissect the complex physicochemical environment, we first conducted a precise characterization of biological tissue as an electrolyte gel. Then, we experimentally evaluated a broad range of 3D staining conditions by using a simplified tissue-mimicking artificial electrolyte gel. The combination of essential conditions allowed a bottom-up design of efficient 3D staining protocol which could uniformly label an adult whole mouse brain, an adult marmoset hemisphere, a ~1 cm^3 tissue block of adult human postmortem cerebellum, and an infant whole marmoset body with dozens of antibodies and cell-impermeant nucleic acid stains. We also demonstrate that our protocol enabled structural and functional neural circuit identification and analysis with Rabies virus tracing and whole-brain c-Fos immunostaining. Therefore, the CUBIC-HistoVIsion pipeline offers advanced opportunities for organ- and organism-scale histological analysis of multicellular systems in the brain and body. [Reference] 1. Susaki et al. Cell 157: 726-739 (2014). 2. Tainaka et al. Cell 159: 911-924 (2014). 3. Susaki et al. Nature Protocols 10: 1709-1727 (2015).

Disclosures: **E. Susaki:** None. **C. Shimizu:** None. **A. Kuno:** None. **K. Tainaka:** None. **X. Li:** None. **K. Nishi:** None. **H. Ono:** None. **K.L. Ode:** None. **Y. Saeki:** None. **K. Miyamichi:** None. **K. Isa:** None. **C. Yokoyama:** None. **H. Kitaura:** None. **M. Ikemura:** None. **T. Ushiku:** None. **Y. Shimizu:** None. **T. Saito:** None. **T.C. Saido:** None. **M. Fukayama:** None. **H. Onoe:** None. **K. Touhara:** None. **T. Isa:** None. **A. Kakita:** None. **M. Shibayama:** None. **H.R. Ueda:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Part

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Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Topic: I.02. Systems Biology and Bioinformatics

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AMED the Basic Science and Platform Technology Program for Innovative Biological Medicine
Grants-in-Aid for Scientific Research (S) (18H05270)
WPI-IRCN program
Grants-in-Aid from the Takeda Science Foundation

Title: Circadian change of whole-brain c-Fos immunoreactivity and its quantitative analysis by CUBIC-neural activity pipeline

Authors: *S. X. YOSHIDA[1], K. MATSUMOTO[1], T. MANO[2], H. FUJISHIMA[1], C. SHIMIZU[2], M. KURODA[2], E. A. SUSAKI[2], H. R. UEDA[2,1];
[1]RIKEN Ctr. For Biosystems Dynamics Res., Osaka, Japan; [2]Dept. of Systems Pharmacology, Grad. Sch. of Medicine, The Univ. of Tokyo, Tokyo, Japan

Abstract: The brain consists of various regions, which are associated with specific sensory, motor, memory, mental and arousal functions. These regions form complex networks and work in a highly interconnected manner. The recent advent of tissue clearing and three-dimensional (3D) imaging techniques potentially enables the understanding of such an organized brain function as a whole, when combined with whole-brain imaging and analysis of immediate early gene expressions[REF: Tatsuki Neuron 2016]. The previous study utilized a transgenic mouse expressing Arc-dVenus transgene reporter for labeling neural activities. However, it usually takes several months to prepare a sufficient number of animals for experiments by multiple crossing. Besides, Arc gene expressions are confined within cortex and hippocampus. To overcome those limitations, we recently developed whole-brain c-Fos immunostaining, imaging, and analysis in combination with CUBIC (Susaki and Mano et al.), which make it possible to analyze the whole brain neural activities with single-cell resolution in a rapid, easy and non-biased manner. Here, we mainly focus on the dynamical change of whole-brain c-Fos expression patterns associated with circadian rhythms to monitor the baseline activities of the brain regions during 24 h. For this purpose, we first analyzed the 3D c-Fos expression patterns in the suprachiasmatic nucleus of the hypothalamus (SCN), a center of the circadian clock in the body.

We collected a series of whole-brain c-Fos immunostaining and imaging data in the dark-dark (DD) condition. Signals of c-Fos in and around SCN were observed with single-cell resolution. Therefore, we are challenging to capture the changes of c-Fos signals quantitatively in and around SCN and expand the analysis to the brain regions throughout the brain. These collections of multiple brain data will provide crucial information on the circadian-related dynamics and state exchange of brain activities. We will finally develop a spatial and temporal atlas of c-Fos activity rhythms throughout 24 h. In this presentation, we report current situations and issues of the CUBIC-neural activity project.

Disclosures: **S.X. Yoshida:** None. **H.R. Ueda:** None. **K. Matsumoto:** None. **H. Fujishima:** None. **T. Mano:** None. **C. Shimizu:** None. **M. Kuroda:** None. **E.A. Susaki:** None.

Poster

520. Molecular Structural Imaging

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Program #/Poster #: 520.14/CC16

Topic: I.02. Systems Biology and Bioinformatics

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Grant-in-Aid for Early-Career Scientists (19K16487)

Title: Ca^{2+}-dependent/-independent hyperpolarization pathway plays a role in sleep regulation - The first application of cubic in sleep research-

Authors: *S. SHI, H. R. UEDA;
The Univ. of Tokyo, Tokyo, Japan

Abstract: The timing and duration of sleep is an evolutionarily conserved process. The sleep-wake cycle accompanies with a global state change in brain and sleep duration seems to be regulated by networks of neural circuits. However, recent reverse and forward genetics have revealed several genes that regulate sleep duration and homeostasis, which suggests that sleep duration is regulated by molecular networks and the sleep-wake cycle might be triggered by a local state change. In this study, we focused a rhythmic firing pattern (slow-wave-sleep firing pattern, SWS firing pattern) with depolarized up states and hyperpolarized down states which are observed in cortical neurons during slow-wave EEG oscillations and attempted to identify

important genes in generating this firing pattern. Considering the tight correlation between SWS firing pattern and slow-wave EEG oscillations as well as behavioral states (e.g. sleep), the genes which are important in generating SWS firing pattern might also play a role in sleep duration regulation. A comprehensive bifurcation analysis against an averaged-neuron model, where a cortical neuron transmits its output to equivalent neurons (i.e., its output returns to itself as input), predicted that Ca^{2+}-dependent/-independent hyperpolarization is associated with SWS (Tatsuki et al 2016, Yoshida et al 2018). To validate the prediction, we generated KO mice for every gene included in the Ca^{2+}-dependent/-independent hyperpolarization pathway and analyzed their sleep phenotypes. As a result, we found that impaired Ca^{2+}-dependent K^+ channels (*Kcnn2* and *Kcnn3*), K^+ leak channels (*Kcnk9*), voltage-gated Ca^{2+} channels (*Cacna1g* and *Cacna1h*), or Ca^{2+}/calmodulin-dependent kinases (*Camk2a* and *Camk2b*) decrease sleep duration, while impaired plasma membrane Ca^{2+} ATPase (*Atp2b3*) increases sleep duration (Tatsuki et al 2016, Yoshida et al 2018). Pharmacological intervention validated the prediction that impaired NMDA receptors (glutamate- and voltage-gated Ca^{2+} channels) reduce sleep duration (Tatsuki et al 2016). CUBIC (Clear, Unobstructed Brain/Body Imaging Cocktails and Computational analysis) and FISH also verified that NMDA receptor down-regulation directly increases the excitability of cortex glutamatergic pyramidal neurons (Tatsuki et al 2016).

Disclosures: **S. Shi:** None. **H.R. Ueda:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.15/DP14/CC17

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.02. Systems Biology and Bioinformatics

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AMED-CREST
AMED Brain/MINDS
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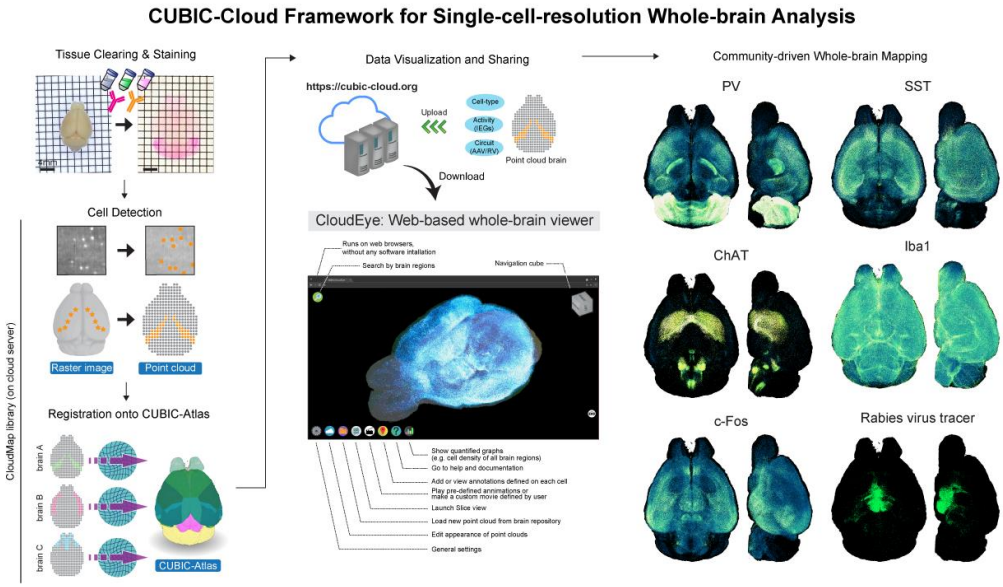
WPI_IRCN program

Title: CUBIC-Cloud: A cloud-based computational framework for quantitative single-cell-resolution whole-brain analysis

Authors: *T. MANO[1,4,5], E. A. SUSAKI[2,5,6], K. MURATA[3,7], K. KON[2], C. SHIMIZU[5], H. ONO[2], K. MIYAMICHI[3,7], K. TOUHARA[3,4,7], H. R. UEDA[2,1,4,5];
[1]Dept. of Information Physics and Computing, Grad. Sch. of Information Sci. and Technolo, [2]Dept. of Systems Pharmacology, Grad. Sch. of Med., [3]Dept. of Applied Biol. Chemistry, Grad. Sch. of Agr. and Life Sci., The Univ. of Tokyo, Tokyo, Japan; [4]Intl. Res. Ctr. for Neurointelligence (WPI-IRCN), Tokyo, Japan; [5]Lab. for Synthetic Biol., RIKEN Ctr. for Biosystems Dynamics Res., Suita, Japan; [6]JST-PRESTO, Saitama, Japan; [7]ERATO Touhara Chemosensory Signal Project, Tokyo, Japan

Abstract: Recent advancements of tissue clearing technologies have offered unparalleled opportunities for researchers to explore the entire neuronal system at cellular resolution. With the expansion of this research paradigm, however, there are ever growing demands for (1) integrated tools to analyze massive 3D images and (2) effective means to exchange whole-brain data, which together would enable community-driven comprehensive brain mapping. To deliver such computational platform, we opted to propose a cloud computing based solution, because of its accessibility, scalability and cost-effectiveness in carrying out intensive computations and connecting massive data. Thus, we designed and implemented CUBIC-Cloud, a cloud-based framework for single-cell-resolution whole-brain analysis. CUBIC-Cloud provides cloud-based image analysis package (CloudMap) which offers web-based graphical interface allowing any users to analyze massive 3D images without requiring expert knowledge on parallel computing. Analyzed data can be visualized and shared with the research community using CloudEye, a web-based whole-brain viewer and database manager. We then demonstrate the generality of CUBIC-Cloud by a variety of applications, including (1) whole-brain analysis of PV, Sst, ChAT, Th and Iba1 expressing cells (2) reconstruction of neuronal activity profile by c-Fos and (3) brain-wide connectivity mapping by pseudo-typed Rabies virus. Together, CUBIC-Cloud offers scalable and community-driven approaches to deconstruct whole-brain architecture.



Disclosures: **T. Mano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); T.M. and H.R.U. hold intellectual copyrights on CUBIC-Cloud software.. **E.A. Susaki:** None. **K. Murata:** None. **K. Kon:** None. **C. Shimizu:** None. **H. Ono:** None. **K. Miyamichi:** None. **K. Touhara:** None. **H.R. Ueda:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); T.M. and H.R.U. hold intellectual copyrights on CUBIC-Cloud software..

Poster

520. Molecular Structural Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 520.16/CC18

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NRF-2017M3C7A1043841
NRF-2017R1D1A1B03035340

Title: Super resolution imaging of various neuronal structures of the brain via expansion microscopy

Authors: ***D.-H. D. SONG**[1], I. C. CHO[1], C. E. PARK[1], J.-Y. SEO[2], Y.-B. SIM[2], K.-B. MIN[2], J.-B. CHANG[1];
[1]KAIST, Daejeon, Korea, Republic of; [2]Sungkyunkwan Univ., Suwon, Korea, Republic of

Abstract: Super-resolution imaging has revealed nanoscale structures of various neuronal structures of the brain. However, the adaptation of super-resolution imaging techniques to the brain is still limited, as it generally requires special chemicals, apparatuses, or skilled personnel. Here, we demonstrate the super-resolution, volumetric, and three-dimensional imaging of various neuronal microstructures of the brain, including blood-brain barrier, synaptic receptors, and neuronal cytoskeletons. Among various super-resolution microscopy techniques, we use expansion microscopy as a imaging modality, as it can easily achieve 60-nm resolution imaging of thick tissue slices with a conventional microscopy system. In this work, we compare the diffraction-limited images and super-resolved images of the same structures to clearly show the nanoscale molecular detailed of those structures that can be revealed only with the super-resolution microscopy technique.

Disclosures: **D.D. Song:** None. **I.C. Cho:** None. **C.E. Park:** None. **J. Seo:** None. **Y. Sim:** None. **K. Min:** None. **J. Chang:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.17/CC19

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: SRFC-IT1702-09
NRF-2017M3C7A1043841

Title: Expansion microscopy imaging of various biomolecular species of the brain

Authors: *I. CHO, J.-B. CHANG;
KAIST, Daejeon, Korea, Republic of

Abstract: Visualizing multiple biomolecular species with nanometer-scale precision can provide essential knowledge to understand the molecular mechanisms of biological phenomenon. In 2015, a new super-resolution microscopy technique, called expansion microscopy, was reported; in this technique, higher lateral and axial resolution are achieved by physically expanding specimens via a swellable hydrogel (ExM; Science 347(6221):534-548, Nat. Biotechnol. 34(9):987-992). Briefly, target specimens, such as cultured cells or tissue slices, are embedded in a swellable hydrogel. During the embedding process, proteins of interest are chemically anchored to the hydrogel. Then, the specimen-hydrogel composite is isotropically expanded in de-ionized water. During the expansion, closely-located proteins move apart, resulting in 60-nm resolution when imaged with diffraction-limited microscopy. Here, we show that multiple biomolecular species of the brain can be visualized with the same resolution via expansion microscopy. We believe that this work will provide richer molecular information of the brain.

Disclosures: I. Cho: None. **J. Chang:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.18/CC20

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NRF-2017M3C7A1043841
NRF-2017R1D1A1B03035340

Title: Super resolution imaging of actin of the brain via expansion microscopy

Authors: *C. PARK, J.-B. CHANG;
KAIST, Daejeon, Korea, Republic of

Abstract: Actin is one of the most essential proteins of cells. In the past, super-resolution microscopy technique, such as STORM or STED, was used to visualize the nanoscale details of actin filaments of cultured cells. However, super-resolution imaging of actin in thick tissue slices is still challenging, as actin is highly expressed in almost all cell types, and it forms a very dense network structure. Here, we demonstrate the super-resolution, volumetric, and three-dimensional imaging of actin and associated proteins of the brain via expansion microscopy. Visualization of actin and various associated proteins of the brain would provide us the molecular information on how the mechanical properties of neurons are regulated and how molecular transportation inside neurons are controlled.

Disclosures: C. Park: None. **J. Chang:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.19/CC21

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: NRF-2017M3C7A1043841
NRF-2017R1D1A1B03035340

Title: Multiplexed super resolution volumetric imaging of substantia nigra via expansion microscopy

Authors: *K. MIN[1], S. KIM[2], Y. CHO[2], J. LEE[2], J. SEO[2], Y. SIM[2], Y. LEE[2], J.-B. CHANG[3];
[1]Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]Sungkyunkwan Universiy, Suwon, Korea, Republic of; [3]KAIST, Daejeon, Korea, Republic of

Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. Among multiple pathological features, the loss of dopaminergic neurons of substantia nigra is the most representative one. However, the molecular details of the loss have not been clearly understood. In this work, we demonstrate the super-resolution, multiplexed, volumetric, three-dimensional imaging of dopaminergic neurons and other associated cells of substantia nigra of the brain via expansion microscopy. To achieve multiplexed, volumetric, and super-resolution imaging of the brain, we screen multiple fluorophores and use the ones yielding the highest brightness. Super-resolution volumetric imaging of dopaminergic neurons and associated cells of the brain would help us to better understand the molecular mechanisms of PD.

Disclosures: **K. Min:** None. **S. Kim:** None. **Y. Cho:** None. **J. Lee:** None. **J. Seo:** None. **Y. Sim:** None. **Y. Lee:** None. **J. Chang:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.20/CC22

Topic: I.01. Molecular/ Biochemical/ and Genetic Techniques

Support: SRFC-IT1702-09
NRF-2017M3C7A104

Title: Multiplexed expansion microscopy imaging of the brain

Authors: *J.-Y. SEO[1], Y.-B. SIM[1], J.-B. CHANG[2];
[1]Sungkyunkwan Univ., Suwon, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of

Abstract: Recently, multiple super-resolution microscopy techniques have been developed and adopted to neuroscience. However, the multiplexing capability of those techniques is limited, as those techniques achieve the higher resolution by precisely-tuning the chemical or physical properties of fluorophores and it is not trivial to tune multiple fluorophores simultaneously. Here, we demonstrate multiplexed super-resolution imaging of the brain based on expansion microscopy. In expansion microscopy, the higher-resolution is achieved by physically expanding specimens themselves, rather than fine-tuning fluorophores. As a result, multiple regular fluorophores can be used together to achieve multiplexed super-resolution imaging. In this work, we show that multiplexed expansion microscopy imaging can be used to reveal the cellular and molecular heterogeneity of the brain.

Disclosures: **J. Seo:** None. **Y. Sim:** None. **J. Chang:** None.

Poster

520. Molecular Structural Imaging

Location: Hall A

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Program #/Poster #: 520.21/CC23

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R00AG044444

NIH Grant DP2EY02798
NIH Grant T32GM088129

Title: Rapid super-resolution imaging of neural tissue with large-scale molecular sampling

Authors: *N. E. ALBRECHT[1], C. G. EBELING[2], R. HOBSON[2], M. A. SAMUEL[1];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Bruker Nano Surfaces, Salt Lake City, UT

Abstract: Proper neural function depends on the correct arrangement and development of synapses, the primary site of communication between neurons. However, the molecular mechanisms that underlie synapse formation and specificity are only partially resolved in part because the internal landscape of synapse protein arrangement remains largely unknown. Two challenges have limited progress towards these goals: 1) synapses are beyond the resolution limit of light, and 2) nanoscopic approaches to visualize synapses are often time consuming and limited in their ability to see multiple proteins at once. To overcome these limitations, we present a rapid and optimized application of Stochastic Reconstruction Microscopy (STORM) for neural tissue that allows us to quickly screen for synaptic protein content and structure from relevant *in vivo* samples. With this workflow, we have successfully prepared tissue for STORM imaging using optimized cryosectioning techniques and imaged synapses and neurons, at nanometer resolution, in tissue sections that are 10µm thick in a protocol that takes 48 hours from tissue harvest to final image. This rapid approach enables high-throughput imaging and screening of neural tissue for the characterization of nanoscale synaptic structures. We are now applying these methods to synapse development and dysfunction to uncover the molecular regulators of synaptic formation and maintenance.

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Poster

521. Optic Probes

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 521.01/CC24

Topic: I.04. Physiological Methods

Support: BMBF, No. 13N13728

Title: Flexible high-density µLED-based implant with improved mechanical and optical performance for optogenetic stimulation of the cochlear

Authors: *E. KLEIN[1], A. DIETER[2], O. PAUL[1], T. MOSER[2], P. RUTHER[1];
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Abstract: This paper reports on the latest achievements for flexible optical implants with integrated micro light-emitting diodes (µLED) on flexible substrates used to stimulate the cochlear neurons [1,2]. Optical cochlear implants (CIs) promise hearing restoration with improved frequency resolution as light can be better focused than electrical stimulation that is used in current clinical CIs. The process flow is based on 6-µm-thick GaN-µLEDs grown and processed on sapphire substrates. The µLEDs are transferred to a carrier wafer [3,4] and subsequently released from the sapphire substrate using a laser-lift-off (LLO) process [4]. The sophisticated wafer-level fabrication process is designed to realize highly flexible implants with up to 144 embedded µLEDs along slender probe shafts with lengths of up to 1.5 cm. To improve mechanical probe performance, the polymer process has been optimized in view of the applied materials minimizing thermo-mechanical stress. This improvement results in a pronounced suppression of implant bending due to pre-stress facilitating its implantation into the cochlea. A selective release mechanism based on a patterned sacrificial layer enables a stress-free probe release increasing the fabrication yield. The optical output power of the µLEDs is improved by roughening the µLED surface using wet etching. The optimized etching parameters enable a low temperature, polymer compatible as wells as time efficient etch process. The surface roughening process increases the optical power by >70%. In order to further improve the output power of the µLEDs, micro lenses and conical concentrators are integrated into the µLED probes. These optical components narrow and focus the emission cone of the µLEDs [5]. The µ-lenses are manufactured by silicone molding while the conical concentrators are integrated into the probe polymer by reactive ion etching. Upon µ-lens assembly, the etched cavities (sidewall angle 70°) are refilled with silicone. The combination of both components raised the light extraction and peak intensity by 115% and 145%, respectively. The capability of the innovative micro-optical probe to stimulate neurons in the cochlea is verified by *in-vivo* recordings from the auditory midbrain. They demonstrate that the optical activation of the auditory pathway with a µLED-based CI overcomes the frequency resolution limit of conventionally applied electrical CIs.

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[3] E. Klein et al., in Dig. Tech. Papers IEEEE MEMS Conf. 2017
[4] E. Klein et al. Frontiers, 47 2014
[5] E. Klein et al., Proc. MEMS Conf. 2019, Seoul

Disclosures: E. Klein: None. **A. Dieter:** None. **O. Paul:** None. **T. Moser:** None. **P. Ruther:** None.

Poster

521. Optic Probes

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 521.02/CC25

Topic: I.04. Physiological Methods

Support: Government of Japan

Title: Real-time visualization of acetylcholine in acute striatal slices using iAChSnFR; a new robust genetically-encoded fluorescent sensor

Authors: *J. A. CHOUINARD[1], J. S. MARVIN[2], P. M. BORDEN[2], L. L. LOOGER[2], J. R. WICKENS[1];
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Abstract: The dawning availability of biosensors able to report the spatiotemporal dynamics of neurotransmitter levels *in vivo* opens new windows on chemical signaling in the brain. These sensors directly and specifically report synaptic signals as they are received by their receptors. A newly developed bacterial periplasmic binding protein (PBP) based acetylcholine (ACh) sensor, iAChSnFR, couples ACh-evoked conformational changes in the PBP to fluorescence changes of a fused, circularly permuted green fluorescent protein. Its high affinity for acetylcholine, millisecond response times, good signal-to-noise ratio, kinetics and targetability makes it suitable for use in live intact preparations. We tested iAChSnFR in acute brain slices after *in vivo* transfection using a CAGFlex AAV viral construct injected in the dorso-lateral striatum of male and female D1-Cre mice. All experiments were approved by the Animal Care and Use Committee of the Okinawa Institute of Science and Technology Graduate University and were conducted in accordance with Japanese law and the Public Health Service Policy on Humane Care and Use of Laboratory Animals of the National Institutes of Health in the United States of America. A minimal period of 4-weeks was allowed for *in vivo* expression, which was stable up to at least 6 months post-transfection. Animals were group housed and showed no abnormal behaviors. Confocal imaging in acute brain slices showed that iAChSnFR successfully detected post-synaptic ACh activity ex vivo. ACh kinetics were recorded following treatments with KCl, ACh and the GABA antagonist bicuculline (BIC) by either bath applications or local micropipette delivery of known concentrations. We observed traveling waves and local oscillations of ACh. Sensor response concentrated at axon plexus regions, displaying high extracellular ACh levels that were extremely responsive to our pharmacological manipulations. The spatiotemporal dynamics of ACh in the striatum are incompletely understood at present. Our data shows that iAChSnFR opens up a way toward a more complete understanding of ACh dynamics in the basal ganglia circuitry. With improved imaging and analysis methods, iAChSnFR could be a useful tool to decipher neural activity into its composite molecular signaling events.

Disclosures: J.A. Chouinard: None. **J.S. Marvin:** None. **P.M. Borden:** None. **L.L. Looger:** None. **J.R. Wickens:** None.

Poster

521. Optic Probes

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Program #/Poster #: 521.03/CC26

Topic: I.04. Physiological Methods

Support: KAKENHI 19H01007
KAKENHI 17H06312
KAKENHI 17K19442
KAKENHI 18J12617
AMED
Brain/MINDS
Takeda Science Foundation

Title: Rational engineering of an intensiometric, genetically encoded, indicator for quantifying CREB phosphorylation events *in vivo*

Authors: *T. YOKOYAMA[1], M. INOUE[1,2], T. ITO[1], Y. KONDO[1], H. FUJII[1], M. SAKAMOTO[1], H. BITO[1,3];
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Abstract: Recent technological advances in genetically encoded calcium indicators (GECIs) now permit tracking of electrical signals in hundreds of neurons *in vivo*. On the other hand, visualizing dynamics of biochemical signals in a large neuronal population *in vivo* remains challenging due to lack of sensitive indicators. Here, we designed and validated a supersensitive, genetically encoded green fluorescent indicator, XCREB-G, which faithfully reported the phosphorylation state of cyclic AMP-responsive element binding protein (CREB), a key transcription factor required for excitation-transcription coupling, at single cell resolution *in vivo*. XCREB-G was expressed in layer 2/3 neurons of the mouse primary visual cortex using an adeno-associated virus (AAV) vector or via in utero electroporation (IUE). Using *in vivo* two-photon microscopy, we directly tested how rapidly and selectively CREB phosphorylation was triggered by visual input-selective stimuli, in hundreds of visual cortical neurons responding to orientation -selective moving gratings. The fastest CREB activation was shown within 10 sec, and the in vivo dynamics of CREB activation was overall consistent with previous reports using cultured neurons. Simultaneous dual-color imaging of calcium (using a red GECI XCaMP-R) and CREB phosphorylation activity (using XCREB-G) demonstrated that a sizable number of neurons showed an orientation-selective CREB activation, following a burst of orientation-selective neuronal activation. More interestingly, we found evidence that a subthreshold CREB activation after a first bout of orientation-selective neuronal activity could lead to a

suprathreshold CREB activation upon a second round of repetitive visual stimuli. Taken together, our findings suggest that nuclear CREB phosphorylation state indeed extracts and integrates information contained in synaptic input events *in vivo*. This technological advance will pave the way to better understand the complex dynamics and information processing elicited in vivo during excitation-transcription coupling, a privileged form of communication between electrical signals and nuclear gene expression via intracellular biochemical reactions.

Disclosures: **T. Yokoyama:** None. **M. Inoue:** None. **T. Ito:** None. **Y. Kondo:** None. **H. Fujii:** None. **M. Sakamoto:** None. **H. Bito:** None.

Poster

521. Optic Probes

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 521.04/CC27

Topic: I.04. Physiological Methods

Support: JSPS KAKENHI JP17H02088

Title: A “plastic” fluorescent probe of neurotransmitter for imaging neurotransmitter secretion in central nervous systems prepared by molecular-imprinting method

Authors: *Y. YOSHIMI[1], N. TESHIMA[1], Y. KATSUMATA[1], K. ENDO[1], R. HASEGAWA[1], T. NAGAHAMA[2], N. HIMI[3], M. OKAMOTO[4], T. INUTSUKA[4];
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Abstract: Analysis of the secretion of neurotransmitters in nervous system is important for elucidating the mechanism of neural network in nervous system. Thus, development of a probe which can track a specified neurotransmitter in real time with high selectivity has been required. Molecularly imprinted polymer (MIP), which is a molecular recognition material obtained by polymerization with a template-effect of the target molecule may be applicable for the probe. In this study, nanoparticle of MIP including fluorescent group (fMIP-NP) were developed as the probe of serotonin. The serotonin, as the template, was immobilized on glass beads by using mixed anchor of 3-aminopropyltrimethoxysilane (shorter chained) and 3- (2-aminoethylamino) propyltrimethoxysilane (longer chained) (1:1 in weight) with glutaraldehyde. The template-immobilized beads were fluidized in a mixed solution of a fluorescent monomer, a template-affinity monomer, and a crosslinking monomer under UV irradiation. The colloidal fMIP-NP was collected from the surface of the beads by washing with dimethylformamide. And the dispersion medium of the colloidal fMIP-NP was replaced with physiological phosphate buffer. The fluorescent intensity and the radius of the fMIP-NP was increased by addition of serotonin

but was insensitive to L-tryptophan which is the analogue of serotonin. The buccal ganglion of *Aplysia* sea snail was stained by the fMIP-NP by soaking in the dispersion. Spike oscillation in the fluorescent intensity were observed at the sensory neurons in the ganglion immediately after the taste of *Nori* seaweed was given to the radula connected with the ganglion. The oscillation was enhanced by addition of an inhibitor of monoamine oxidase which collects serotonins from the synapses. The results indicate that the serotonin secreted from neurons can be detected by imaging technology using the fMIP-NP templated by serotonin as a probe. Most of transmitters can be targets of MIPs, thus imaging with probes of fMIP-NPs would enable analysis of dynamism of neurotransmitters in central nerve system.

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Poster

521. Optic Probes

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Topic: I.04. Physiological Methods

Support: DP1EY024503
R01EY011787
R01NS110422
R01MH115900
The Uehara Memorial Foundation, Research Fellowship

Title: Simultaneous detection of spikes and synaptic potentials with two-photon, two-color voltage and calcium imaging *in vivo*

Authors: *Y. BANDO[1,2], M. WENZEL[3,2], R. YUSTE[2];
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Abstract: As a dream experiment, measuring simultaneously synaptic potentials and action potentials from populations of neurons could enable to better understand neuronal computations, as this would capture both the inputs and outputs of all the cells in a neural circuit. However, this has been difficult to achieve using conventional electrophysiological techniques. As a step towards measuring synaptic inputs and spikes in neuronal populations, we previously tested existing genetically-encoded voltage indicators (GEVIs) with two-photon (2P) imaging *in vivo*, and found that ArcLight-MT could detect subthreshold voltage change *in vivo* (Bando et al., Cell

Reports, 2019). However, its signal-to-noise ratio (SNR) was not large enough for reliable detection of synaptic potentials. Here, we modified ArcLight-MT, developing SynVolS (Synaptic Voltage Sensor), as a voltage indicator specialized to detect subthreshold synaptic inputs. We also added a soma-targeting signal peptide to improve its SNR (SynVolS-ST). We found that SynVolS-ST could detect subthreshold membrane potential change more accurately than ArcLight-MT with 2P imaging *in vivo*. We then co-expressed SynVolS-ST with jRGECO1a, a red calcium indicator, and performed simultaneous 2P voltage and calcium imaging *in vivo*. Using this method, we successfully recorded putative synaptic inputs and action potentials from multiple neurons simultaneously. As a practical application, we also used 2P SynVolS-ST voltage and jRGECO1a calcium imaging to pharmacological epilepsy model, and found different dynamics of propagation of voltage and calcium transients under seizures. In conclusion, we have rationally designed SynVolS as a specialized probe for subthreshold potentials measurements, and combined it with jRGECO1a to perform two-photon, two-color voltage and calcium imaging, successfully detecting both spikes and synaptic potentials *in vivo*. This technique could be useful to large-scale analysis of input-output relationship during sensory processing, learning and decision making in awake behaving animals.

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Poster

521. Optic Probes

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 521.06/CC29

Topic: I.04. Physiological Methods

Title: Optimization of genetically encoded voltage indicators for *in vivo* imaging

Authors: *I. KOLB, A. ABDELFATTAH, B. ARTHUR, G. CAO, V. JAYARAMAN, D. KIM, W. KORFF, L. LAVIS, Y. LIANG, L. LOOGER, D. MERRYWEATHER, D. REEP, E. SCHREITER, Y. SHUAI, K. SVOBODA, A. TSANG, G. TSEGAYE, G. TURNER, A. WONG, J. HASSEMAN;
Janelia Res. Campus, Ashburn, VA

Abstract: Measuring millisecond-scale activity of multiple individual neurons *in vivo* is a key technology for studying signal processing in neural circuits. Genetically encoded voltage indicators (GEVIs) are promising tools because they directly sense neuronal membrane voltage and report both action potentials and subthreshold fluctuations in spatially resolved groups of neurons. However, because of limitations of existing GEVIs and the short durations of voltage signals, it has been challenging to image voltage in intact tissue, especially in densely-labeled populations of neurons. Imaging membrane potential dynamics in subcellular compartments has also remained out of reach. We used a high-throughput mutagenesis and screening pipeline to

improve the sensitivity of existing GEVI scaffolds for *in vivo* imaging. We screened >10,000 variants of ASAP1 in HEK cells and 1,500 in dissociated neurons and discovered variants that have a two-fold improved $\Delta F/F_0$, as well as a variant with high sensitivity in the hyperpolarization and subthreshold activity range. The top-performing variants were tested by patch-clamp in cultured neurons and were found to exhibit improved performance compared to other ASAPs. The variants had sufficient $\Delta F/F_0$ and signal-to-noise ratio to report action potentials *in vivo* under one-photon and two-photon illumination in mouse visual cortex. The addition of a soma-targeting sequence further improved *in vivo* signal fidelity. We additionally screened 3,400 variants of the chemigenetic GEVI, Voltron (Abdelfattah *et al* Science 2019). Several mutations conferred a two-fold improvement in $\Delta F/F_0$ over the original scaffold without sacrificing fast kinetics.

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Poster

521. Optic Probes

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Topic: I.04. Physiological Methods

Support: CIHR FS-154310
NSERC PGSD2-519229-2018

Title: Engineering red and far-red genetically encoded Ca^{2+} indicators

Authors: *R. DALANGIN, Y. SHEN, R. E. CAMPBELL;
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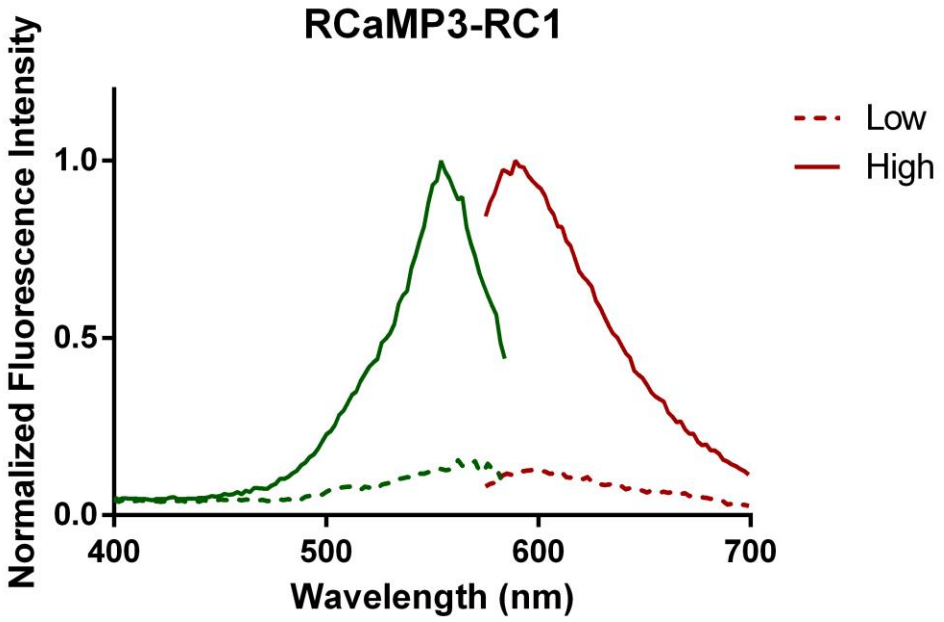
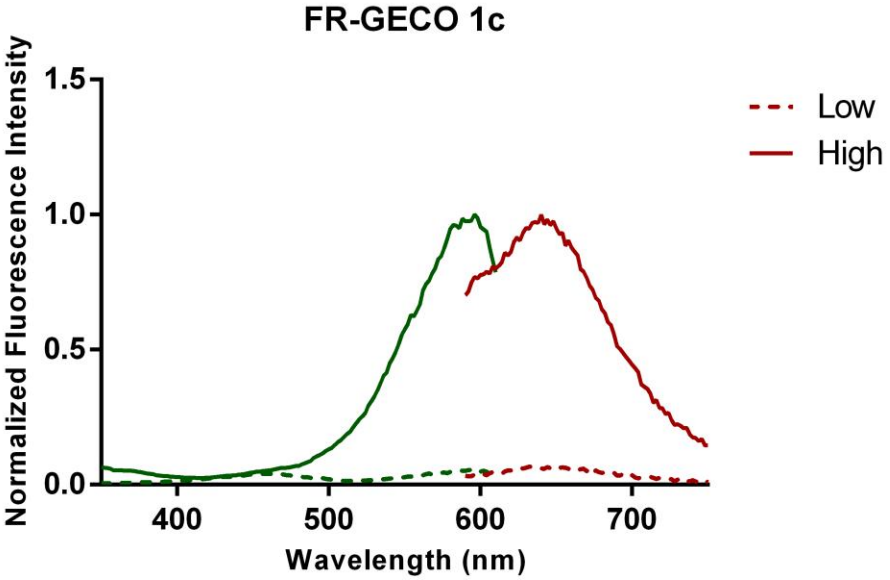
Abstract: Genetically-encoded calcium ion (Ca^{2+}) indicators (GECIs) make up an integral part of the optogenetics toolbox, enabling direct measurement of Ca^{2+} dynamics across small and large populations of neurons. The green GCaMPs represent the peak of CI engineering; however, red GECIs are more desirable as their longer excitation and emission wavelengths enable deeper penetration into the brain. Additionally, red GECIs can be used with other indicators for simultaneous multicolour imaging of multiple analytes. Currently, while there are multiple red GECIs, there is no red GECI that matches the performance of the best GCaMP variants in all criteria, and efforts are ongoing to produce bright red GECIs with large dynamic ranges, fast kinetics, good photostability and minimal cytotoxicity. Here, we present our work on

engineering two series of red GECIs, RCaMP3 and the Far Red (FR)-GECOs. RCaMP3 is an updated version of the RCaMP series using mRuby3, one of the brightest red fluorescent proteins to date. Preliminary results indicate that RCaMP3 has a larger dynamic range and higher affinity than jRCaMP1b. The FR-GECO series, which is based on the far-red fluorescent protein mKelly, is a more red-shifted line of red GECIs, with excitation peaks 600 nm and emission peaks ~640 nm. Our variants show high affinity for Ca^{2+} with dynamic ranges ranging from 7-fold to 18-fold response to Ca^{2+}. We anticipate that these GECIs will be valuable additions to the available repertoire of genetically-encoded fluorescent biosensors.





Disclosures: **R. Dalangin:** None. **Y. Shen:** None. **R.E. Campbell:** None.

Poster

521. Optic Probes

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Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 521.08/CC31

Topic: I.04. Physiological Methods

Support: NIH Grant U01 NS103517

Title: Improved genetically encoded indicators for multi-spectral fluorescent voltage imaging

Authors: ***M. KANNAN**[1], G. VASAN[1], C. HUANG[2], S. HAZIZA[2], X. LIU[1], C. GARDINER[1], M. J. SCHNITZER[2], V. A. PIERIBONE[1];
[1]The John B Pierce Lab., Yale Univ., New Haven, CT; [2]Stanford Univ., Stanford, CA

Abstract: Recent advances in technologies such as single-cell transcriptomics and genetic tools are propelling neuroscientists to probe brain function with the finest detail possible. While newer cell types are being uncovered, newer approaches to access these distinct cell types are also being described. The field is now in active pursuit of functional tools to study the dynamic interplay of these individual cell types as they act concertedly to influence network activity and behavior. Here, we describe the development of multicolor genetically encoded voltage indicators (GEVIs) and the optical instrumentation for studying spiking dynamics in distinct cell types, simultaneously, in live animals. As recording tools, GEVIs exhibit clear advantages over electrode-based approaches and Ca^{2+} imaging. Like Ca^{2+} imaging, but unlike electrodes, GEVIs enable functional readouts at high-throughput, unambiguous identification of recorded cell types and longitudinal access to identified neurons in chronic preparations. But surpassing Ca^{2+} imaging, GEVIs offer millisecond-scale temporal resolution and report voltage oscillations, subthreshold activity and hyperpolarizations with much greater fidelity. FRET-opsin GEVIs combine the superior kinetics of opsins with enhanced brightness of engineered fluorophores. The newest members of this advanced generation, Ace-mNeon and Varnam, immaculately capture spike waveforms in live animals under routine imaging conditions. We further improve the dynamic range of these sensors and deliver them to individual cell types using intersectional strategies to study the dynamics of neural microcircuits in mice and flies. By expanding their applications to monitor activity across multiple cell populations, we will maximize their potential to behave as surrogate electrodes in neuroscience research.

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Poster

521. Optic Probes

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Program #/Poster #: 521.09/CC32

Topic: I.04. Physiological Methods

Support: DARPA: N6600117C4012

Title: Engineering calcium- and voltage- sensitive bioluminescent systems for *in vivo* imaging in brain

Authors: S. SUNITA[1,2], *J. PLATISA[1,2], P. O'BRIEN[1], K. TRIEBEL[1], M. CONNOR[1], C. GARDINER[1], J. CHOI[3], A. J. TAAL[3], J. D. FABBRI[3], K. SHEPARD[3], V. A. PIERIBONE[1,2]; [1]The John B Pierce Lab., New Haven, CT; [2]Yale Univ., New Haven, CT; [3]Columbia Univ., New York, NY

Abstract: Bioluminescence is the production of light in many organisms that is mediated by an enzyme-substrate (luciferase-luciferin) reaction. This phenomenon is used by diverse species such as marine animals, bacteria and fungi to serve myriad functions (defense, predation and mating). For optical imaging, bioluminescence is emerging as an attractive alternative to traditionally used fluorescent approaches as it shows low background, high sensitivity and does not require an illumination source. The last decade has seen a surge in targeted protein engineering to enhance native luciferase properties alongside the synthesis of stable substrate homologs, making bioluminescent systems useful for a wide variety of imaging applications. In this work, we focus on development of calcium- and voltage- sensitive bioluminescent indicators that will allow for *in vivo* imaging of neuronal activity at cellular resolution. To this end, we have targeted a recently published firefly luciferase derivative that produces red-shifted glow-type bioluminescence ($\lambda_{max}$of ~650 nm) when combined with a modified substrate. Our current strategy is to introduce calcium- or voltage-sensitive sequences, amino acid substitutions and linker-length deletions within the native enzyme to produce probes capable of recording neuronal activity with optimal spatiotemporal resolution. High-throughput *in vitro* characterization of these modified probes is performed by differential scanning fluorimetry and luminometer assays to provide key information on pH and thermal stability. The newly developed constructs have also been assayed for calcium or voltage sensitivity through systematic screening in human embryonic kidney cells and neurons. We used adeno-associated viral vectors for expression of the most promising mutants in the mouse brain, followed by *in vivo* imaging of neuronal activity using commercially available EMCCD cameras or novel, custom-made implantable lensless imaging systems.

Disclosures: **S. Sunita:** None. **J. Platisa:** None. **P. O'Brien:** None. **K. Triebel:** None. **M. Connor:** None. **C. Gardiner:** None. **J. Choi:** None. **A.J. Taal:** None. **J.D. Fabbri:** None. **K. Shepard:** None. **V.A. Pieribone:** None.

Poster

521. Optic Probes

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Topic: I.04. Physiological Methods

Support: NIH 1R21 EY027562
NIH F31 EB024378-01A1
NIH T32 GM008275

Title: Exploiting intra-protein electron transfer for optimal temporal resolution in *de novo* designed genetically encoded voltage indicators

Authors: *M. J. IWANICKI[1], C. MOSER[1], B. Y. CHOW[2], B. DISCHER[1];
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Abstract: Developing probes that can monitor voltage signaling events on the sub-microsecond timescale and can be targeted to specific cells and membranes is crucial to advance our understanding of the communication between neurons. Organic voltage sensitive dyes can report changes in membrane potential on appropriate timescales with high sensitivity; however, they cannot be genetically targeted to specific cell types. This lack of targetability is solved by using genetically encoded voltage indicators (GEVIs). GEVIs are typically constructed from the voltage-sensing domain of natural proteins, but they tend to be dimmer and slower than organic voltage sensitive dyes. Here, we present our progress on the development and characterization of a new family of genetically encoded voltage indicators called THOR (Transmembrane Hemoprotein Optical Reporter), a fusion protein of a *de novo* designed transmembrane 4-α-helical protein and a fluorescent optical reporter. THORs bind heme in the core of the 4-α-helical bundle, and the heme oxidation states change as a function of the transmembrane electric field. The oxidation state of one of the heme cofactors is then reported via FRET by an optical reporter, i.e. the fluorescent protein mOrange2. The speed of THORs is dependent on electron transfer between the cofactors, and therefore, tunable by their distance. Our simulations revealed that we will be able to achieve µs responses. A water-soluble prototype of THOR expressed in E. coli undergoes 18% fluorescent quenching of mOrange2 upon heme reduction. Several different variants of THOR were designed with two different lengths: one that closely matches the thickness of the membrane and one that extends into the cytoplasm. THORs have been expressed in both HEK293t cells and rat hippocampal neurons. The trafficking of THORs into plasma

membrane of HEK293t cells was improved with the sequential addition of export tag sequences from the potassium ion channel, Kir2.1. We have confirmed that THORs in rat hippocampal neurons decrease their fluorescence upon membrane potential changes induced by addition of valinomycin.

Disclosures: **M.J. Iwanicki:** None. **C. Moser:** None. **B.Y. Chow:** None. **B. Discher:** None.

Poster

521. Optic Probes

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 521.11/CC34

Topic: I.04. Physiological Methods

Support: NSF Grant 1707359
McNair Medical Institute at the Robert and Janice McNair Foundation

Title: JEDIs - improved genetically encoded voltage indicators for imaging membrane potential dynamics

Authors: Z. LIU[1], X. LU[1], Y. GOU[2], S. GUAN[2], J. LEE[1], E. FROUDARAKIS[2], J. REIMER[3], A. S. TOLIAS[3], *F. ST-PIERRE[2];
[1]Rice Univ., Houston, TX; [3]Neurosci., [2]Baylor Col. of Med., Houston, TX

Abstract: A longstanding goal in neuroscience is to understand how spatiotemporal patterns of neuronal electrical activity underlie brain function, from sensory representations to decision making. An emerging technology for monitoring electrical dynamics is voltage imaging using Genetically Encoded Voltage Indicators (GEVIs) — light-emitting protein indicators whose brightness directly reports voltage. GEVIs are promising tools for monitoring voltage dynamics at high spatiotemporal resolution in genetically defined cell types *in vivo*. Indicator performance has steadily progressed since GEVIs were first reported; they have also been deployed in multiple animal systems. However, despite significant progress made so far by the GEVI community, the performance of current voltage indicators is usually insufficient for robust single-trial two-photon imaging of voltage dynamics of many individual neurons in behaving rodents. As a result, GEVIs have yet to be broadly adopted.
The mechanisms of voltage indicators are insufficiently understood to enable purely rational engineering of new GEVIs with predictable outcomes, motivating the evaluation of many candidates to identify improved variants. As screening by patch-clamp electrophysiology can only evaluate fewer than ~10 new candidates per day, we are developing a pipeline for high-throughput screening of GEVI libraries, followed by detailed characterization of the most promising candidates. Here, we will present our ongoing efforts to develop improved methods for screening GEVIs, using indicators of the Accelerated Sensor of Action Potential (ASAP)

family as a starting point. We also present preliminary data on promising candidates identified during our screens, which are now referred as Jellyfish-derived Electricity-reporting Voltage Indicators (JEDIs). We anticipate that these efforts will ultimately produce high-performing indicators of broad utility for imaging spontaneous voltage dynamics in the brains of behaving animals.

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Poster

521. Optic Probes

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Program #/Poster #: 521.12/CC35

Topic: I.04. Physiological Methods

Support: CIHR FDN-143209
Brain Canada for the Canadian Neurophotonics Platform
Brain Canada Multi-Investigator Research Initiative

Title: Comparison between transgenic and AAV-PHP.eB mediated expression of GCaMP6s using *in vivo* wide field functional imaging of brain activity

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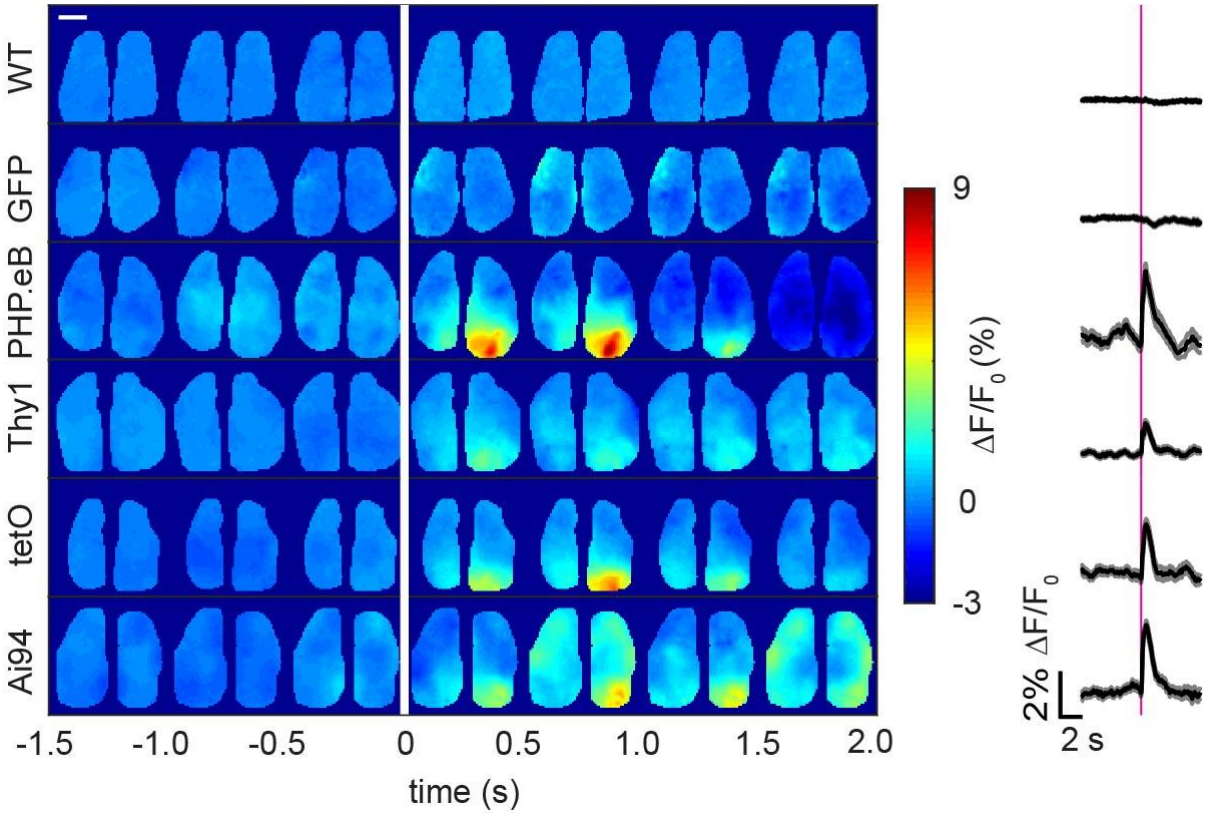
Abstract: Mesoscale imaging of genetically encoded activity sensors, such as GCaMP6, is a powerful approach to assess cortical activity and functional connectivity *in vivo*. Expression of GCaMP6 in mice is typically achieved using transgenic models or by intracerebral injection of viral vectors. Recently, blood brain barrier (BBB) permeable adeno-associated virus (AAV) variants, AAV-PHP.B and AAV-PHP.eB, have been developed, allowing for widespread transduction of neural cells using non-invasive intravenous (IV) delivery. Currently, no comparison between this expression strategy and other classical transgenic approaches has been conducted. In this study, GCaMP6s was expressed in the cortex of negative C57BL/6J mice (n=3) using tail-vein injection of the AAV.PHP.eB viral vector under a pan-neuronal human synapsin promoter; and fluorescence, responsiveness, and connectivity mapping performance were compared against three transgenic lines: Thy1-GCaMP6s (n=4), TITL-GCaMP6s (n=3), and tetO-GCaMP6s (n=3) and two reference lines (negative, n=2 and GFP, n=2). GCaMP expression strategies were compared using transcranial wide field single-photon imaging in awake head fixed animals. Epifluorescence brightness of PHP.eB mediated expression was comparable to Thy1-GCaMP6s, but dimmer than tetO-GCaMP6s and TITL-GCaMP6s. Peak $\Delta F/F_0$ response to visual flash stimuli was evaluated between expression strategies (Fig 1).

Further, spontaneous variations and regionally correlated activity maps calculated from resting-state activity were compared between expression strategies. We show that expression strategies employing the BBB permeable virus, AAV-PHP.eB, yield comparable expression and function as those derived from transgenic mice. We recommend single photon wide-field imaging of visual responses in awake mice IV injected with AAV-PHP.eB for the testing of new genetically engineered activity sensors.

Fig 1: Visually evoked maps showing dorsal cortex activity for control and GCaMP6s expressing animals (left), and $\Delta F/F_0$ time series in corresponding visual area (right).



Disclosures: **N. Michelson:** None. **M. Vanni:** None. **T. Murphy:** None.

Poster

521. Optic Probes

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

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Title: Imaging acetylcholine dynamics by GPCR-based fluorescent indicators

Authors: *M. JING[1], Y. LI[4], J. ZENG[2], M. XU[5], Y. LI[3];
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Abstract: Acetylcholine (ACh) regulates diverse physiological processes throughout the body, yet further deciphering the function and regulation of cholinergic transmission requires precise monitoring of ACh *in vivo*. By tapping into the natural-evolved ACh sensing GPCRs as the scaffold, we previously developed the first genetically-encoded ACh sensors (GACh2.0) with sub-second kinetics, high molecular specificity as well as physiological-relevant affinity in detecting ACh. To further improve GACh sensors, we conducted site-directed mutagenesis to optimize the residues at the interface between GPCR and cpGFP, which resulted in an improved version of GACh sensors, named GACh3.0. Comparing with the GACh2.0 sensor, GACh3.0 shows significant increase in fluorescence response to ACh, while still retain fast kinetics and high molecular specificity. Taking advantage of the sensitive GACh3.0 sensor, we successfully tracked the dynamics of endogenous ACh release in *Drosophila* olfactory system in response to multiple physiological-relevant stimuli. We further real-time monitored the ACh release in hippocampus of mice during sleep-awake cycles by fiber photometry recording system. Finally, using the miniature two-photon microscope, we achieved the imaging of locomotion-induced cortical ACh dynamics in free-moving mice. In sum, the new GACh sensor provide a convenient, broadly applicable tool for monitoring cholinergic transmission underlying diverse biological processes.

Disclosures: **M. Jing:** None. **Y. Li:** None. **J. Zeng:** None. **M. Xu:** None. **Y. Li:** None.

Poster

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Title: Spying on purinergic transmission by constructing new genetically encoded adenosine and ATP sensors

Authors: *Z. WU[1,2], H. WANG[1,2], K. HE[1,2], M. JING[1,2,3,4], S. PAN[1,2,3], H. WU[5], M. XU[6,7], Y. LI[1,2,3,4];
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Abstract: Purinergic transmitters, e.g. adenosine (Ado), ADP and ATP, are playing important roles in a plethora of physiological processes, including sleep-wake control, learning and memory, cardiovascular activity and immune response. Malfunction of the purinergic signaling is implicated in diseases such as pain, epileptic seizures and drug addiction. A major obstacle to decipher the function of purinergic transmission is the lack of a direct, sensitive, and non-invasive method to monitor structurally similar purinergic transmitters, ideally with high spatial and temporal resolutions *in vivo*. Here by tapping into human Ado and P2Y receptors, we developed a toolbox of genetically-encoded G-protein coupled Receptor Activation Based (GRAB) fluorescent sensors, with unique molecular specificity for Ado, ADP, ATP and UTP. Purinergic GRAB sensors have good plasma membrane localization and exhibit robust fluorescence increases upon cognate ligand binding, as well as inheriting their parental purinergic receptors' binding specificity and affinity. Using $GRAB_{Ado}$, we successfully monitored electrical and high-KCl stimulation evoked increases of extracellular Ado level in cultured hippocampal neurons. Aided by fiber photometry, we successfully detected the dynamic change of Ado levels during chemical induced seizures and sleep-awake cycles in mice *in vivo.* Furthermore, using $GRAB_{ATP}$, we successfully observed the mechanical-stimulation or laser ablation evoked ATP signals in astrocytes *in vitro* and *in vivo*. In sum, the development of purinergic GRAB sensors provides critical genetically-encoded imaging probes for investigating purinergic transmission in physiological and pathological processes with molecular specificity.

Disclosures: Z. Wu: None. **H. Wang:** None. **K. He:** None. **M. Jing:** None. **S. Pan:** None. **H. Wu:** None. **M. Xu:** None. **Y. Li:** None.

Poster

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The General Program Natural Science Foundation of China (project 31371442)
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Title: Development and applications of the novel genetically-encoded serotonin sensors

Authors: *M. LI[1], J. WAN[2], M. JING[2], J. FENG[3], J. ZOU[5], J. ZENG[4], X. LI[1], C. WEI[6], H. WANG[1], Y. ZHENG[1], F. DENG[1], M. LUO[7], S. TANG[1], Y. LI[1];
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Abstract: Serotonin (also called 5-HT) is an important monoamine neuromodulator, critical for regulation of sleep, appetite control as well as learning and memory. Malfunction of 5-HT may result in depression, addiction, compulsivity and other neurological disorders. One major obstacle to understanding the physiological regulation of 5-HT is lack of sensitive methods to track the dynamics of 5-HT non-invasively with good cell specificity and high temporal resolution, especially *in vivo*. Here, for the first time, we developed a genetically-encoded 5-HT sensor by coupling cpEGFP with a human 5-HT receptor. Upon 5-HT binding, the chimeric receptor changes its conformation which leads to a subsequent fluorescent signal increase from the embedded cpEGFP, therefore reporting 5-HT. We named this sensor "the GPCR Activation Based sensor for 5-HT, or $GRAB_{5\text{-}HT}$. With iterative engineering, we developed a series of $GRAB_{5\text{-}HT}$ sensors with high specificity and sensitivity. Furthermore, we demonstrated $GRAB_{5\text{-}HT}$ could be applied in multiple organisms, including *Drosophila*, mice and monkey for reliable detection of 5-HT *in vivo*. Thus, this tool would enhance our understanding of complex neuromodulation in health and in diseases.

Disclosures: **M. Li:** None. **J. Wan:** None. **M. Jing:** None. **J. Feng:** None. **J. Zou:** None. **J. Zeng:** None. **X. Li:** None. **C. Wei:** None. **H. Wang:** None. **Y. Zheng:** None. **F. Deng:** None. **M. Luo:** None. **S. Tang:** None. **Y. Li:** None.

Poster

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NIH brain initiative grant NS103558

Title: Development of a toolbox of genetically-encoded fluorescent sensors for endocannabinoids and neuropeptides

Authors: *H. WANG[1,2], A. DONG[3,2], T. QIAN[1,2], S. PAN[3,2], K. HE[1,2], D. J. LIPUT[4], H. L. PUHL, III[5], B. DUDOK[6], D. M. LOVINGER[8], I. SOLTESZ[7], Y. LI[1,2,3,9];
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Abstract: Endocannabinoids (eCBs) and neuropeptides are essential signaling molecules in both nervous and endocrine system. By modulating on the related brain circuits, these molecules are the key regulators for many neural processes, including social behavior, sleep and circadian rhythm, food ingestion and pain sensation. Monitoring these neuromodulators' dynamics in live animals allow us to understand their diverse functions in both physiological and pathological status. eCBs mediate pre-synaptic inhibition by retrograde transmission, a process that is often hijacked by the recreational usage of marijuana to exert psychoactive experiences among human. Neuropeptides are synthesized and packaged in large-dense-core vesicles and their secretion dynamics, which remains largely unknown, is greatly different from that of the canonical synaptic vesicles. Currently, one major impediment to decipher the function and secretion dynamics of eCBs, as well as other neuropeptides, is the lack of direct, sensitive and non-invasive tools to monitor these compounds *in vivo*, with high spatial and temporal resolutions. Here by tapping into their innate G protein-coupled receptors (GPCR), we developed a toolbox of genetically-encoded fluorescent sensors for eCBs, cholecystokinin (CCK), vasoactive

intestinal peptide (VIP), somatostatin (SST), vasopressin/oxytocin, ghrelin and orexin. These novel fluorescent sensors utilize GPCR receptors as the ligand sensing modules and circular-permutated GFPs as the optical output. These sensors have good membrane localization and exhibit robust fluorescence increase (up to 700% $\Delta F/F_0$) upon cognate ligand application, when expressed in cultured neurons. In addition, these sensors retain the molecular specificity and affinity of the native receptors and have minimal downstream G protein coupling, compared to their original GPCR scaffolds. The eCB sensor could detect the evoked eCB release through electric stimulation in acute mouse brain slice from striatum, and enable to monitor the dynamics of eCB wave during epilepsy in the hippocampus of live mice. We plan to further validate these peptide sensors mentioned above in slice & *in vivo* and extend the sensor development strategy to cover all known peptide GPCRs in human genome. These novel eCB and neuropeptides sensors can be powerful molecular tools that lead to a deeper understanding of the physiological- and pathophysiological- roles of eCB and neuropeptides transmission.

Disclosures: H. Wang: None. **A. Dong:** None. **T. Qian:** None. **S. Pan:** None. **K. He:** None. **D.J. Liput:** None. **H.L. Puhl:** None. **B. Dudok:** None. **D.M. Lovinger:** None. **I. Soltesz:** None. **Y. Li:** None.

Poster

521. Optic Probes

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Program #/Poster #: 521.17/CC40

Topic: I.04. Physiological Methods

Support: NIH R01NS109794-01
NSF CBET-1848029

Title: *In vivo* population voltage imaging of neural activity in awake, behaving mice

Authors: *S. N. SHROFF[1], H.-A. TSENG[1], H. J. GRITTON[1], S. BENSUSSEN[1], K. D. PIATKEVICH[2], M. F. ROMANO[1], E. S. BOYDEN[2], X. HAN[1];
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Abstract: The basal ganglia circuit has long been recognized as an important regulator for movement in the brain. Dysfunction of this circuit can result in motor disorders such as Parkinson's and Huntington's disease. The striatum, the largest nucleus of the basal ganglia, is critical for normal motor control and is implicated in the pathology of various movement disorders. Recently, it has been reported that striatal neurons are modulated during movement and that spatially clustered striatal neurons may encode similar aspects of movement. Current techniques fall short of demonstrating how striatal neurons contribute to and modulate motor output, due to the inability to record both spiking and subthreshold activity from multiple cells

simultaneously during movement. Here, we report a novel genetically-encoded voltage sensor, SomArchon, which exhibits millisecond response times and compatibility with optogenetic control, and which increases the sensitivity, signal-to-noise ratio, and number of neurons observable, by several-fold (to approximately a dozen neurons at once) over previously published reagents. Under conventional one-photon microscopy, SomArchon enables population analysis of neural activity, both at subthreshold and spiking levels, in multiple brain regions—cortex, hippocampus, and striatum—of head-fixed awake, behaving mice. Using SomArchon in the striatum, we detected both positive and negative responses of striatal neurons during movement, previously reported by electrophysiology but not easily detected using modern calcium imaging techniques, highlighting the power of voltage imaging to reveal bidirectional modulation. We also observed that adjacent neurons did not respond to movement speed in identical ways. SomArchon may thus help disambiguate activity amongst spatially clustered striatal neurons.

Disclosures: **S.N. Shroff:** None. **H.J. Gritton:** None. **H. Tseng:** None. **S. Bensussen:** None. **K.D. Piatkevich:** None. **M.F. Romano:** None. **E.S. Boyden:** None. **X. Han:** None.

Poster

521. Optic Probes

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Program #/Poster #: 521.18/CC41

Topic: I.04. Physiological Methods

Support: NIH Director's Office 1DP2NS082126
NINDS 1R01NS081716
NINDS 1R01NS087950-01
Grainger Foundation
Pew Foundation
Boston University Biomedical Engineering Department
NIH R01NS109794-01

Title: Voltage imaging of subthreshold dynamics in awake behaving mice

Authors: *H.-A. TSENG[1], S. BENSUSSEN[1], K. D. PIATKEVICH[2], S. SHROFF[1], H. GRITTON[1], R. MOUNT[1], J. SHERMAN[1], E. S. BOYDEN[2], X. HAN[1];
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Abstract: Proper brain functions require highly coordinated activities among large groups of pre- and postsynaptic neurons. Many studies have demonstrated precisely timed interactions between spiking activity and local field potential (LFP) oscillations during behaviors. However, how subthreshold intracellular membrane voltage dynamics of individual neurons impact spike

timing in the brain remains largely unclear. *In vivo* intracellular recording has provided some valuable information, but often with one neuron being recorded at a time. On the other hand, calcium imaging can capture dynamic changes of intracellular calcium concentrations of individual neurons from a large population of neurons, but lacks the temporal resolution of individual spikes, let alone subthreshold voltage activities.
Here we demonstrate the capability of a newly developed voltage sensor, SomArchon, in recording subthreshold voltage dynamics *in vivo* with wide-field microscope. With SomArchon, we are able to simultaneously observe the activities from multiple neurons in awake behaving animal, while recording LFPs at the same time. We examined individual neurons' spike timing relative to their own intracellular membrane voltage oscillations or to LFP oscillations, and found that, in most neurons, spikes were more phase-locked to intracellular oscillations than to LFP oscillations. We further calculated the coherence of intracellular oscillations among simultaneously recorded neuron pairs, and compared that to the coherence between intracellular oscillations and LFP oscillations. We noticed a great heterogeneity in coherence, and coherence of intracellular oscillations between neuron pairs show larger variations than that between intracellular oscillations and LFP oscillations. Together, these results demonstrate that SomArchon enable the analysis of subthreshold dynamics in awake behaving mice brains, and open up new frontiers on understanding the significance of subthreshold oscillations in neural network computation and behavior.

Disclosures: H. Tseng: None. **S. Bensussen:** None. **K.D. Piatkevich:** None. **S. Shroff:** None. **H. Gritton:** None. **R. Mount:** None. **E.S. Boyden:** None. **X. Han:** None. **J. Sherman:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.01/CC42

Topic: I.04. Physiological Methods

Support: NIH Grant R01DC014044

Title: Recessed traces for low-stress passivation of chronic penetrating silicon microelectrodes

Authors: *N. NOLTA, P. GHELICH, M. HAN;
Univ. of Connecticut, Storrs, CT

Abstract: Implantable microelectrode arrays are important tools for neuroscientific research and clinical neuroprosthetics, yet despite decades of research and development, reliable multi-year functionality remains elusive. One commonly observed failure mode is degradation of passivation materials. Passivation materials electrically isolate the conducting traces from each

other and the saline environment, and additionally provide a barrier against water and ions which corrode silicon and metals. Various passivation materials have been tried, including silicon oxide, silicon nitride, polyimide, Parylene, and SU-8, but all are vulnerable to degradation. However, material composition is not the only factor influencing materials degradation; mechanical stress can also play a role. Indeed, there is evidence to suggest that the non-planar topography created by conducting traces creates stress concentrations that become weak points for degradation. Therefore, we developed a method for recessing traces within the substrate, flush with the wafer surface, so that overlying passivation layers are planar. The traces were 5-10 µm wide, up to 6 mm long, 400 nm thick, and planar within ± 10 nm of the wafer surface. The technique is self-aligned and requires no additional masks or polishing steps. Furthermore, we incorporated the technique into the fabrication process of our multi-site, multi-shank silicon electrode array designed for 3D stimulation of cochlear nucleus and found no negative impact on connectivity or impedance *in vitro*. Accelerated soak testing is in progress to determine whether devices with recessed traces are more resistant to corrosion than controls.

Disclosures: **N. Nolta:** None. **P. Ghelich:** None. **M. Han:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

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Program #/Poster #: 522.02/CC43

Topic: I.04. Physiological Methods

Support: NIH Grant R01DC014044

Title: A portable neurostimulator with wirelessly adjusted constant-current waveforms and bias voltage

Authors: *A. ERSOZ[1], H. PHU[1], I. KIM[2], M. HAN[3];
[1]Univ. of Connecticut, Storrs, CT; [2]Dept. of Med., Univ. of Connecticut, Farmington, CT;
[3]Biomed. Engin. Dept., Univ. of Connecticut, Storrs, CT

Abstract: Neural interface electronics are essential in stimulation and recording of neuronal activities. Off-the-shelf and application specific integrated circuits (ASICs) approaches are common ways to design portable or implantable neurostimulator and recording systems. Typical off-the-shelf neurostimulator electronics are constructed from multiples of printed circuit boards (PCBs), connected with connectors, which may consume power and space. On the other hand, ASICs are time-consuming to design and incur high non-recurring engineering costs. We developed a compact embedded system using off-the-shelf components and 32-bit ARM® microprocessor to generate constant-current waveforms with wireless control of anodic voltage bias that enhances charge injection. The six-layer in a single board PCB (four signal and two

power plane layers) has the microprocessor controlled by a user-interface via Bluetooth and programmed with ARM® Keil® µVision®5 IDE and STM32CubeMX ToolChain. We integrated two 3.7 V Li-Ion rechargeable batteries and a power management block regulating at 3.3V, 5V, and -5V. Fabricated PCB had dimensions of 64.13 mm × 52.56 mm × 7.68 mm. In benchtop testing, stimulation signals were generated constant-current waveforms and resulting voltage transients were monitored to ensure safety stimulation. Evoked neural response recording circuit was successfully validated by a Plexon headstage testing unit whose signals were filtered, amplified, and analyzed. The user interface transmitted and received wirelessly, including stimulation parameters such as amplitude and polarity of biphasic signals. In particular, anodic bias voltages were adjusted remotely via Bluetooth which was not available in earlier work. Furthermore, it consumes slightly less power in active mode than other published off-the-shelf systems. We showed that the system could perform constant-current waveforms generation, Bluetooth communication, channel switching, and neural recording, all on a single PCB with off-the-shelf components. Additional testing with microelectrodes *in vitro* and *in vivo* are underway, and this portable neurostimulator system may ultimately be used in behavioral experiments.

Disclosures: **A. Ersoz:** None. **H. Phu:** None. **I. Kim:** None. **M. Han:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.03/CC44

Topic: I.04. Physiological Methods

Support: NIH R01DC014044

Title: Comparison of sputtered iridium and sputtered iridium oxide on silicon-based neural microelectrodes

Authors: *P. GHELICH, N. NOLTA, M. HAN;
Univ. of Connecticut, Storrs, CT

Abstract: Neural microelectrodes have small electrode sites that allow for spatially-selective stimulation and recording, however these small site areas impose demanding constraints on the materials used. The ideal electrode material needs to have low impedance, high charge injection capacity, high mechanical/chemical stability, batch fabrication, and high biocompatibility. Two of the most extensively-validated materials *in-vivo* are sputtered iridium and sputtered iridium oxide film (SIROF). Previous studies have characterized the effects of various deposition conditions on each of these film's characteristics, but few have compared these materials head-to-head while keeping the geometry of the electrode sites constant. Here, we fabricated silicon microelectrodes designed for penetrating auditory brainstem and midbrain with electrode sites

55x37 um or 110x37 um coated with DC magnetron reactively-sputtered iridium deposited under pure argon, 1:4 oxygen:argon, or 1:1 oxygen:argon flow rates at 4 mTorr deposition pressure. Films were characterized using x-ray photoelectron spectroscopy, scanning electron microscopy, optical microscopy, focused ion-beam scanning electron microscopy, and electrochemical measurements including cyclic voltammetry, current pulsing, and electrochemical impedance spectroscopy in phosphate buffered saline at pH 7. Results confirmed stable and uniform film deposition thanks to a titanium adhesion layer. Electrochemical measurements confirmed functionality of the devices is in the expected range, although there were differences for each film depending on its oxygen content. This comparison will enable researchers to screen for the ideal film for their application and further refine vacuum-based deposition conditions for neural applications.

Disclosures: P. Ghelich: None. **N. Nolta:** None. **M. Han:** None.

Poster

522. Techniques: Microelectrodes II

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Program #/Poster #: 522.04/CC45

Topic: I.04. Physiological Methods

Support: NIH SPARC Award OT2OD024907
NSF Award 1707316

Title: Acute intraganglia recordings of single-unit neural activity with a novel microelectrode array

Authors: E. C. BOTTORFF[1,2], A. A. JIMAN[1,2,4], E. J. WELLE[1,2], P. R. PATEL[1,2], J. P. SEYMOUR[3,1], C. A. CHESTEK[1,2,3], *T. M. BRUNS[1,2];
[1]Biomed. Engin., [2]Biointerfaces Inst., [3]Electrical and Computer Engin., Univ. of Michigan, Ann Arbor, MI; [4]Electrical and Computer Engin. Dept., King Abdulaziz Univ., Jeddah, Saudi Arabia

Abstract: Currently, the standard electrodes for recording from the peripheral nervous system are extraneural and are generally only capable of detecting compound action potentials. Commonly used intraneural devices are relatively large and can cause severe tissue responses, which are non-ideal for a chronic devices. The demand for advanced neural interfaces that can provide highly selective stimulation and recording is growing. Previously, we developed arrays of neuron-sized 8-µm carbon fibers for cortical interfacing, obtaining long-term, high-fidelity single unit recordings with minimal to no histological response. We are translating these carbon fiber microelectrode arrays (CFMAs) to peripheral interfaces. CFMAs (200-250 µm length, 132 µm pitch, 2x8 fiber layout) were inserted into sacral dorsal root ganglia of anesthetized felines. Procedures are also being developed for CFMA insertion into other species and ganglia, such as

rodent major pelvic ganglia. Neural activity was recorded for various stimuli, including cutaneous brushing, bladder volume modulation, distal electrical stimulation, and spontaneous activity.
Unique unit waveforms across CFMA fibers were observed for various stimuli. Signal amplitudes of up to 350 µV peak-to-peak were detected. Bladder units with a firing rate correlation coefficient to bladder pressure of up to 0.97 were observed in multiple experiments. We also determined that CFMAs can withstand multiple insertions, allowing for repositioning within an experiment.
These acute experiments demonstrate the potential of CFMAs for single-unit specificity in peripheral nerve interfacing. Further work, including the development of mounting and attachment procedures, are necessary before these arrays can be evaluated in survival experiments.

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Poster

522. Techniques: Microelectrodes II

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Topic: I.04. Physiological Methods

Support: National Institute of Health SPARC Program (Award OT2OD024907)
National Science Foundation (Award 1707316)

Title: Monitoring of glucose- and insulin-triggered vagus nerve activity using carbon fiber microelectrode arrays in anesthetized rats

Authors: *A. A. JIMAN[1,2,4], E. J. WELLE[1,2], P. R. PATEL[1,2], E. C. BOTTORFF[1,2], D. C. RATZE[2,3], J. M. RICHIE[1,2], Z. OUYANG[1,2], D. YAN[3], L. L. ZIMMERMAN[1,2], J. P. SEYMOUR[1,3], C. A. CHESTEK[1,2,3], T. M. BRUNS[1,2];
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Abstract: Glucose regulation is a vital continuous process for maintaining a healthy biological state. This requires complicated coordination between the endocrine and nervous systems. An important pathway in the peripheral nervous system for glucose regulation is the vagus nerve, as it connects the relevant organs in glucose regulation to the central nervous system. However, limited information is available on the neural activity for glucose regulation that propagates through the vagus nerve. An electrode that has shown promising neural recording abilities with minimal tissue damage in the brain is the carbon fiber microelectrode array (CFMA). We

hypothesized that a modified version of the CFMA with sharpened fibers can capture glucose regulation neural activity in the vagus nerve. In this study, we performed non-survival experiments on anesthetized, female Sprague-Dawley rats. Through a midline ventral cervical incision, the left vagus nerve was isolated and placed on a custom 3D-printed nerve-holder. A CFMA (10-16 fibers; 200-250 µm in length; 132 µm pitch; 2-row layout) was inserted in the vagus nerve and connected to a neural interface processor that recorded at a sampling rate of 30 kHz. A bolus of glucose (1 g), or insulin (8 U) was administered intraperitoneally to modulate blood glucose levels. Measurements of blood glucose concentrations from the tail were obtained every 5 minutes using a glucometer. Glucose administration elevated blood glucose levels by 60.6%. Approximately 2 minutes after glucose administration, an initial unit with an average amplitude of 72.2 µV peak-to-peak began firing at a rate up to 24 spikes/sec. This initial unit may represent afferent activity due to the detection of the glucose bolus. Around 30 minutes after glucose administration, larger units with amplitudes over 140 µV peak-to-peak occurred at peak firing rates above 30 spikes/sec. These units may be efferent vagus nerve activity to the liver to modulate glucose storage and production, as reported in the literature. Insulin administration decreased blood glucose levels by 22.4%. Neural units were observed 15 minutes after administration, with average amplitudes over 160 µV peak-to-peak, and peak firing rates above 45 spikes/sec. This activity may be afferent signals to increase glucose intake. Overall, our results demonstrate that CFMA is a viable electrode for recording neural unit activity for glucose regulation in the vagus nerve. Furthermore, this study suggests that the CFMA can be used to monitor neural unit activity in peripheral nerves to help better understand the neural regulation pathways in various physiological and pathophysiological conditions.

Disclosures: **A.A. Jiman:** None. **E.J. Welle:** None. **P.R. Patel:** None. **E.C. Bottorff:** None. **D.C. Ratze:** None. **J.M. Richie:** None. **Z. Ouyang:** None. **D. Yan:** None. **L.L. Zimmerman:** None. **J.P. Seymour:** None. **C.A. Chestek:** None. **T.M. Bruns:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.06/CC47

Topic: I.04. Physiological Methods

Support: NIH 1OT2OD024907
NINDS 1U01NS094375
NINDS 1UF1NS107659
NSF 1707316

Title: Fabrication and characterization of a carbon fiber peripheral nerve electrode appropriate for chronic recording

Authors: *E. J. WELLE[1], A. A. JIMAN[1], P. R. PATEL[1], J. WOODS[2], J. M. RICHIE[1], E. C. BOTTORFF[1], J. P. SEYMOUR[2], T. M. BRUNS[1], C. A. CHESTEK[1];
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Abstract: State-of-the-art intraneural peripheral nerve electrodes are large, silicon-based structures that cause a large histological response and are ill-suited for recording from small autonomic nerves. The focus of this work is to adapt our minimally-scarring carbon fiber electrodes for brain to a chronic intraneural nerve array. We aim to increase the durability of the carbon fiber electrodes to withstand the surgical handling necessary for nerve implantation, while maintaining a cellular scale electrode that can insert through epineurium. Toward that end, we embedded carbon fibers in silicone to increase robustness, sharpened the fibers to penetrate epineurium, and tested fibers coated with poly(3,4-ethylene-dioxythiophene):sodium p-toluenesulfonate (PEDOT:pTS) *in vivo*.

We tested the durability of carbon fibers by embedding uninsulated fibers in a body of silicone and inducing a 90-degree bend to simulate the expected shear forces seen during surgery. We found that fibers of 175µm length were robust to thousands of bend cycles. After 3000 bends, 15 of 16 fibers remained intact. We blunt cut carbon fibers using a 532nm green laser and inserted fibers into silicone of stiffness similar to epineurium to determine a length for *in vivo* testing. We found that blunt fibers reliably insert into silicone without breaking when less than 200µm in length (N=8 fibers). We hypothesized that sharpened fibers would insert into tissue more easily, and therefore sharpened fibers with a 3mm butane flame when protruding from the surface of water. The dimensions of sharpened fibers were 224µm in length with 147µm of exposed carbon and a tip angle of 72 degrees (N=24 fibers).

We inserted functionalized sharpened carbon fibers coated with PEDOT:pTS into peroneal and cervical vagus nerves of anesthetized rats (N=5 arrays, 71 fibers, 7 animals). In all experiments, we observed that the sharpened carbon fiber electrodes penetrated the epineurium for successful insertion. The average 1kHz impedance of coated fibers prior to and upon insertion was 38kΩ and 56kΩ, respectively. In both cases, the Z_{1kHz} of roughly 90% of fibers measured below 100kΩ. We recorded spontaneous and evoked neural activity in each experiment and are analyzing the data for discernable single units. We also inserted sharpened fibers into anesthetized feline sacral dorsal root ganglia (N=3) and confirmed insertion with evoked neural recordings and 1kHz impedances (Z=59kΩ).

This work shows that the durable nature of csarbon fibers embedded in silicone can withstand surgical handling and insert into various types of nerves. Our next step will be the fabrication of an array for chronic implantation.

Disclosures: E.J. Welle: None. **A.A. Jiman:** None. **P.R. Patel:** None. **J. Woods:** None. **J.M. Richie:** None. **E.C. Bottorff:** None. **J.P. Seymour:** None. **T.M. Bruns:** None. **C.A. Chestek:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.07/CC48

Topic: I.04. Physiological Methods

Support: NIH U01 NS099697-01
NSF GRFP DGE-1644868

Title: Design and testing of an active 4096 channel micro-electrocorticography (μECoG) array

Authors: *G. SHULL[1], J. VIVENTI[1], J. ROGERS[2], J.-K. CHANG[3], J. LI[3], E. SONG[3];
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Abstract: Electrocorticography (ECoG) is used clinically for evaluation prior to epilepsy surgery. High-density micro-electrocorticography (μECoG) provides the ability to resolve finer features of local field potentials from the cortex. Additionally, μECoG can be used to record action potentials from the cortex if the electrodes are smaller than ~250 μm^2. However, creating small, dense electrodes limits recording area and electrode channels due to constraints imposed by individually wired electrodes.

Active μECoG arrays use transistor multiplexing at the recording site to scale the number of channels without scaling the number of wires, which enables high-density recordings without compromising recording area. Fabricating transistors in university cleanrooms adds significant noise that limits the density of active μECoGs. Advances in post processing commercial CMOS devices opens the door to designing smaller transistors and more elaborate circuit architectures on the electrodes that can be used to create dense, high-channel-count, low-noise arrays. Encapsulating the arrays in thermally-grown silicon dioxide extends electrode lifetime to several years.

This work describes the design, simulation, and testing of a (4,096 channel) μECoG array with an electrode area of 15 μm x 15 μm, a pitch of 50 μm, and a recording area of 3.5 mm x 3.5 mm. To determine the smallest size of transistors that would perform with suitable noise and gain performance, we simulated noise, gain, and parasitics of transistor widths and electrode architectures including a source follower amplifier. We then designed and laid out the array and sent it to the foundry for production.

We plan to post process the device from the foundry and attach it to a polyimide substrate to achieve a total array thickness of 25 μm. We will use bench testing to quantify noise and gain performance of the array, *in vitro* soak testing to quantify lifetime of the array, and *in vivo* acute experiments of rat auditory cortex to asses frequency decoding capability of the array. We hypothesize the array will increase decoding accuracy.

This electrode array will expand the capabilities of μECoG, enabling chronic, high-channel-count recording from the cortex with low noise, and high resolution.

Disclosures: G. Shull: None. **J. Viventi:** None. **J. Rogers:** None. **J. Chang:** None. **J. Li:** None. **E. Song:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.08/CC49

Topic: I.04. Physiological Methods

Support: SBIR Grant 1R43NS102067-01A1

Title: High density, actively multiplexed μECoG array (HDAMA)

Authors: *I. RACHINSKIY[1], L. WONG[2], C.-H. CHANG[1], C. WANG[1], M. TRUMPIS[1], J. OGREN[2], Z. HU[2], B. MCLAUGHLIN[3], J. VIVENTI[1];
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Abstract: Background: The study of brain function involves observation of coordinated firing from populations of neurons that spread across large brain regions. Sensing of electrical signals from dispersed neurons is vital for neuroscience research and can aid in the understanding of mechanisms of brain function and for the treatment of brain disorders. There emerges a demand for highly conformal devices, which span large cortical regions and have sufficient spatial resolution, chronic recording capability, and a small implantation footprint. We, therefore, developed an actively multiplexed electrode array using soft material to capture the fine spatiotemporal information on the cortical surface. **Method:** We have designed a high density, actively multiplexed μECoG array (HDAMA) using a reinforced silicone substrate that is ultra-soft, highly conformal, and resilient to repetitive mechanical strain. 61 electrode contacts are arranged in an 8 × 8 array covering ~3.4 × 3.4 mm^2 area. Electrode contacts are made of bulk PtIr to ensure low impedance and biocompatible, chronic implantability. We also developed a miniaturized custom integrated circuit multiplexing chip housed in a near-hermetic package within the ultra-thin (<500μm) silicone nano-mesh electrode array, to allow high-channel count multiplexing at the implant site. The longevity of silicone electrodes was evaluated by *in vitro* soak testing in PBS at 60℃, resulting in about five-fold aging acceleration compared to body temperature. We also implanted the HDAMA over the rat auditory cortex and compared the performance of signal quality to previous publications. **Results:** *In vitro* accelerated soak testing of the electrode demonstrated projected robustness for over a year. Electrodes maintained impedance values of 5-15kΩ throughout 3 months of accelerated soaking (15 month *in-vivo*

equivalent). The recording capabilities of the device in both acute and chronic animal experiments displayed an evoked auditory response from all 61 channels both during surgery and for the following 30 days in a chronically implanted subject. Analysis of the *in-vivo* auditory-evoked response yielded 60% decoding accuracy (chance level, 8%) during intra-operative recordings and comparable accuracy to past publications [BM1] in chronically implanted animals. The multiplexing IC and data acquisition system showed comparable performance to a single-chip Intan RHD 2164 recording system, but with far fewer connector wires. By combining the electrode and the multiplexing chip into a unified near-hermetic silicone package, we will produce an electrode array with direct multiplexing capability through a system-on-chip approach.

Disclosures: I. Rachinskiy: None. **L. Wong:** None. **C. Chang:** None. **C. Wang:** None. **M. Trumpis:** None. **J. Ogren:** None. **Z. Hu:** None. **B. McLaughlin:** None. **J. Viventi:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.09/CC50

Topic: I.04. Physiological Methods

Support: NIH Grant U01 NS099697-01
DARPA Grant BAA-16-09
NSF Grant CCF-1564051

Title: Kiloscale neural interfaces for long-term recording

Authors: *C. CHIANG[1], S. M. WON[2], A. L. ORSBORN[3], K. YU[4], M. TRUMPIS[1], B. BENT[1], C. WANG[1], B. PESARAN[5], J. A. ROGERS[2], J. VIVENTI[1];
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Abstract: Background: Long-lived, high-throughput neural interfaces are essential for precise brain mapping and high-performance neuroprosthetic systems. Ultra-thin (< 30 μm), flexible electrode arrays can maintain signal quality over long periods of time with little tissue injury or irritation after implantation. Electrode arrays that sample neural activity densely, such as those used in micro-electrocorticography (μECoG), reveal rich spatial and temporal information hidden by traditional approaches such as electroencephalography (EEG) and conventional ECoG. Scaling such devices to sample over a thousand sites across a relevant centimeter-scale brain region requires integrating powered electronics into the device. Active electrode arrays

(with integrated, powered electronics) can enable such kiloscale sampling by multiplexing many electrode sites to only a few external wire connections. However, existing active electrode arrays largely rely on encapsulation strategies that have limited implant lifetimes. To solve this problem, we have incorporated a thin layer of silicon dioxide (SiO_2) to act as the dielectric medium for capacitive sensing and as the bio-fluid barrier. This flexible, active µECoG array provides stable and long-term (over a year) neural recording from rat auditory cortex. A scaled version of this array with 1,008 electrodes captured detailed spatiotemporal patterns across sensorimotor cortices from a non-human primate (NHP).
Methods: Actively-multiplexed, capacitive arrays were fabricated using an in-house transfer printing process. The kiloscale array included 1,008 electrodes, with a sensing area of 9 × 9.24 mm^2. The rodent array included 64 electrodes, implanted epidurally over rat auditory cortex. The overall device was ~25 µm thick. The biofluid barrier and capacitive sensing dielectric was provided by a 900nm thick layer of thermally grown SiO_2 (t-SiO_2). Decoding of 13 different auditory pure-tone stimuli was used to measure the long-term performance of the neural interface in rats.
Result: We present evoked responses and decoding performance for over one year of implantation in five rats. Leakage current remained below cutoff for the duration of the implants. The long-term signal performance is similar to passive, faradaic electrodes, except for additional noise added by the transistors. Implanted arrays showed stable performance over the entire implantation period. This work demonstrates the feasibility of using a ultra-thin layer of t-SiO_2 as the dielectric medium for capacitive sensing of neural signals and as the biofluid barrier, with a projected lifespan up to 60 years.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.10/CC51

Topic: I.04. Physiological Methods

Support: Rainwater Foundation

Title: An approach for functional validation of connectivity in neuronal networks

Authors: *E. GUZMAN[1], K. R. TOVAR[3], K. S. KOSIK[2];
[1]MCDB, [2]Univ. of California Santa Barbara, Santa Barbara, CA; [3]Neurosci. Res. Inst., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Intracellular electrophysiological recordings using patch-clamp from pre and postsynaptic neurons have been invaluable in helping to describe the ways that a neuron responds to input stimulus and has revealed many of the adaptive phenomena that neurons exhibit when exposed to changing stimulus intensity. Local field potential recordings of neuronal activity using multi-electrode array (MEA) devices offers the opportunity to perform high throughput studies of electrophysiological networks from cultured neurons. MEA's have been used extensively to try to infer functional connectivity of random neuronal networks through the use of several statistical techniques. However, methods to validate such statistical techniques on MEA's has relied heavily on simulated data and fails to validate the real biological network connectivity. Our results demonstrate that multi-electrode arrays can be used to quantify functional connectivity of cultured mouse neurons. We outline 2 methodological approaches for quantification based on passive recordings and employing extracellular stimulation. We perform physical and pharmacological manipulations on cultures that result in quantifiable changes to interactions between detected units. These approaches are advantageous over previously described method(s) since there is no patch-clamp is required to identify or validate connectivity allowing for higher-throughput connectivity measurements. Finally, this method is generalized enough that it can be applied to recordings most commercial MEA's currently available.

Disclosures: E. Guzman: None. **K.R. Tovar:** None. **K.S. Kosik:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.11/CC52

Topic: I.04. Physiological Methods

Support: NINDS 1U24NS109043

Title: Real-time processing and visualization of high-channel-count electrophysiology data with the open ephys GUI

Authors: *P. KULIK[1], A. DOSHI[1], A. CUEVAS LOPEZ[2], J. VOIGTS[3], J. H. SIEGLE[4]; [1]Allen Inst., Seattle, WA; [2]Dept. de Ingeniería Electrónica, Univ. Politècnica De València, Valencia, Spain; [3]Brain and Cog. Sci., MIT, Cambridge, MA; [4]Allen Inst. for Brain Sci., Seattle, WA

Abstract: The Open Ephys Graphical User Interface (GUI) is an open-source, cross-platform, plugin-based application for acquiring multichannel electrophysiology data (open-ephys.org/gui). It is designed to facilitate experiments involving closed-loop feedback, which require custom event detection algorithms and a flexible data processing pipeline. Open Ephys is currently used by hundreds of scientists in over 30 countries, and has a vibrant community of

researchers contributing to its development (github.com/open-ephys/plugin-GUI). We have recently adapted the Open Ephys GUI for use with Neuropixels, a new type of silicon probe capable of recording single unit activity across dozens of cortical and subcortical structures simultaneously. We are currently working on optimizing this software for large-scale electrophysiological recordings—up to 6144 channels—by improving the efficiency of the signal-processing pipeline and creating novel visualizations for high-dimensional data streams. With funding from a BRAIN Initiative U24 award, we will provide community-wide support for the software, including simplifying the installation process, enhancing available documentation and tutorials, and creating a centralized repository for sharing and downloading plugins. This repository will host user-contributed plugins, written in C++ or Python, that extend the capabilities of the core application. The plugin architecture makes it straightforward to create modules that interface with different types of recording devices, giving the Open Ephys GUI the potential to be compatible with a wide variety of high-channel-count silicon probes.

Disclosures: **P. Kulik:** None. **A. Doshi:** None. **A. Cuevas Lopez:** None. **J. Voigts:** None. **J.H. Siegle:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.12/CC53

Topic: I.04. Physiological Methods

Title: A low-power wireless transmission system of neural data by hardware compression

Authors: *A. CUEVAS LOPEZ[1], D. R. QUIÑONES[2], E. PÉREZ[1], V. J. LÓPEZ MADRONA[1], J. VOIGTS[3], J. H. SIEGLE[4], S. CANALS[1], D. MORATAL[2];
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Abstract: Experiments involving freely-moving animals have become increasingly important in recent times. They allow for more complex set-ups than their stationary counterparts and make it possible to study more natural behaviours. One of the biggest technical limitations for such experiments is the need to handle cabling from the headpieces to the acquisition equipment. Recently, there have been developments on electrophysiology headstages capable of transmitting neural data wirelessly. The main limitation of these technologies is power consumption due to the large amount of data being transmitted, usually either requiring large batteries for prolonged operation or limiting acquisition to fewer channels or lower rates than wired systems.
We have developed a wireless headstage focusing on low power and reduced size while maintaining characteristics similar to regular wired headstages. Our current prototype is able to

acquire 16 channels at 200KS/s while consuming less than 150mA, while targeting a size under 9mm^2. To that avail, we have designed a compression algorithm that reduces the amount of data to be transmitted up to 40% of its original size, thus reducing power requirements proportionally. The compression algorithm has been designed to run in an Igloo nano device, an ultra-low power, small-footprint FPGA from Microsemi, which also controls the chip responsible for neural acquisition. Due to its packaging of 25mm^2, the selected device allows for miniaturized designs. The overhead current consumption for the compression algorithm in this specific device has been measured in less 1mA. To transmit data from the FPGA to the wireless controller, we have developed a packet-based communication protocol focused on minimizing memory requirements. This protocol allows the wireless transmitter to use lower power datagram-based schemes while maintaining signal integrity in case of transmission errors.
The decompression algorithm has been developed as a plugin for the Open Ephys GUI, an open source electrophysiology suite that provides a perfect framework to visualize, analyze and record the neural signals acquired by the headstage.

Disclosures: **A. Cuevas Lopez:** None. **D.R. Quiñones:** None. **E. Pérez:** None. **V.J. López Madrona:** None. **J. Voigts:** None. **J.H. Siegle:** None. **S. Canals:** None. **D. Moratal:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

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Program #/Poster #: 522.13/CC54

Topic: I.04. Physiological Methods

Support: Arnold O. Beckman Postdoctoral Fellowship Award
Burroughs Wellcome Fund
U.S. Army Research Laboratory and Defense Advanced Research Projects Agency

Title: A non-contact multi-channel probe for monitoring network electrophysiology

Authors: ***T. SHARF**[1], M. HARI[1], Z. CHENG[2], L. PETZOLD[2], P. HANSMA[3], K. S. KOSIK[1]; [1]Neurosci. Res. Inst., [2]Computer Sci., [3]Physics, Univ. of California Santa Barbara, Santa Barbara, CA

Abstract: In the field of modeling and treating neurological and psychiatric disease, the goal of scientists is to have efficient and cost-effective assays of multi-cellular electrophysiology. Observing electrical activity of large multi-cellular populations with single-cell resolution is a crucial step towards uncovering basic principles that govern their function, which may transform our understanding of and approach to treating disease. (For example, over the course of the past two decades over US $1 billion has been invested on clinical trials which have ultimately failed

to produce effective drugs treatments for Alzheimer's disease.) Current state-of-the-art multi-cellular *in vitro* electrophysiology technologies require individual cell cultures to be grown on expensive electronic devices that often degrade at the cell-sensor interface. These difficulties introduce significant batch-batch variability and affect overall long-term cell viability, making it a challenge to generate reliable statistics. This variability has impeded the progress of developing effective pre-clinical models of disease *in vitro*. To solve this problem, we have developed a new electrophysiology technology that can measure extra-cellular fields generated by neurons in a non-contact configuration and resolve the electrical foot-print of an arbitrary number of neuron cultures grown on disposable glass coverslips, rapidly, reliably and in succession without degrading its sensitivity or performance. Our technology that could serve to dramatically improve the development of assays to aid in screening the effectiveness of human drug responses at the preclinical level using patient derived neurons from human induced pluripotent stem (iPS) cells.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.14/CC55

Topic: I.04. Physiological Methods

Title: All-diamond microfiber electrodes for neurochemical sensing

Authors: *C. A. RUSINEK[1], Y. GUO[2], R. RECHENBERG[3], E. PURCELL[2], C. MCKINNEY[4], M. BECKER[3], W. LI[2];
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Abstract: Developments in microelectrode technology has enabled deeper understanding of brain and nervous system function. The small size and low capacitance allow microelectrodes to sense neurotransmitters (NTs) at rapid rates on the sub-second time scale. These measurements have traditionally been executed using fast scan cyclic voltammetry (FSCV) with carbon-fiber microelectrodes (CFMEs). While CFMEs have exhibited the properties needed for *in vivo* neurochemical sensing, the need for a stable, batch-fabricated, and up-scalable microelectrode remains. Diamond is a material which exhibits excellent fabrication flexibility in conjunction with many other advantageous electrochemical properties such as good biocompatibility, low background current, and wide potential window. In this work we demonstrate the analytical capability of a novel, all-diamond microfiber (μ-fiber) electrode for neurochemical sensing. The all-diamond electrodes consist of a conductive boron-doped diamond (BDD) core encapsulated

by insulating layers of un-doped polycrystalline diamond (PCD). Analysis by scanning electron microscopy (SEM) revealed overall dimensions of 6 μm high x 25 μm wide and ~2 mm in length with an electroactive surface area of roughly 70 μm^2. The diamond μ-fibers were electrochemically characterized using model redox analytes such as ferri/ferrocyanide ($Fe(CN)_6^{3-/4-}$) and ruthenium hexaamine ($Ru(NH_3)_6^{2+/3+}$), among others; excellent steady state response was observed for each analyte using cyclic voltammetry (CV). The diamond μ-fibers were then assessed for their ability to several clinically-relevant analytes, including multiple NTs. Multiple FSCV parameters were investigated such as waveform, scan rate, and potential range. These were completed using the High Definition Cyclic Voltammetry (HDCV) interface developed at the University of North Carolina Chapel Hill. These novel all-diamond μ-fiber electrodes have commercial-scale potential, generating a powerful tool for neurochemical analysis.

Disclosures: C.A. Rusinek: None. **Y. Guo:** None. **R. Rechenberg:** None. **E. Purcell:** None. **C. McKinney:** None. **M. Becker:** None. **W. Li:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.15/CC56

Topic: I.04. Physiological Methods

Title: Microfabricated diamond microfiber electrodes for neural sensing

Authors: Y. GUO[1], C. H. THOMPSON[2], W. YANG[1], R. RECHENBERG[3], C. RUSINEK[3], M. BECKER[3], E. K. PURCELL[2], ***W. LI**[1];
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[3]Fraunhofer USA Inc. Ctr. for Coatings and Diamond Technologies, East Lansing, MI

Abstract: Mapping brain circuitry is one of the greatest scientific challenges currently facing the neuroscience community, and developing new technologies with improved electrical and chemical signal detection from single neurons is a critical step to achieve this grand goal. Microelectrode implantation, as a practical approach, has shown promising feasibility for neuronal recording. Recently, our group has developed an all diamond microfiber electrode, consisting of a conducting boron-doped polycrystalline diamond (BDD) fiber encapsulated by an insulating microcrystalline diamond (MCD) shell. The diamond microfiber was fabricated by chemical vapor deposition (CVD) of thin MCD and BDD films on a silicon wafer. Both layers were plasma etched using a Cu mask to form microfibers. A sealing layer of MCD was selectively grown on the patterned fibers, except for the contact pads where a Ti/Cu mask was applied to inhibit diamond growth. After being released from the Si substrate, the tip of the fiber was laser cut to expose the BDD electrode. Building upon our prior work, this work presents the experimental characterization of the as-fabricated diamond fibers using bench-top and *ex vivo*

methods. In particular, electrochemical impedance spectroscopy was used to measure the impedance of the fiber over broadband. The electrodes show low 1kHz impedance of less than 200 kΩ, indicating the high conductivity of heavily doped CVD BDD. The stability of MCD packaging was evaluated using an accelerated aging test in phosphate-buffered saline (PBS) and 10-20 mM H_2O_2/PBS solution that mimics acute post-surgery inflammatory reaction, for up to 7 days at 87 °C in absence of light. *Ex vivo* electrophysiology validates the efficacy of the diamond microfiber for extracellular recording of single unit response in neural culture. Future work will focus on *in vivo* validation of device functionalities for single unit recording in living brain tissues.

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Poster

522. Techniques: Microelectrodes II

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Program #/Poster #: 522.16/CC57

Topic: I.04. Physiological Methods

Title: A wearable, high channel count, digitizing, neural signal amplifier for microelectrode recordings in humans

Authors: *N. R. HALPER[1], C. DRYDEN[1], M. SORENSON[1], M. GERHARDT[1], F. SOLZBACHER[2], R. FRANKLIN[1];
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Abstract: The BRAIN Initiative sets out seven primary areas for researchers all of which have some dependency on electrophysiology as a primary method of further understanding the brain. Particularly, the new focuses of the BRAIN Initiative are on applications in human health and ability. As part of the call to map the brain in new, holistic ways, new electrode technologies are emerging and scientists are pushing towards larger channel counts to sample greater numbers of areas of the brain simultaneously. Electrophysiology equipment, such as amplifiers and recording systems, need to be created to meet the needs of researchers seeking BRAIN Initiative goals.
Microelectrodes targeting cortical or deep brain structures are required for understanding circuit dynamics in the human brain. Current technologies limit researchers to lower channel counts that restrict the understanding of circuit interactions or regional interactions in the brain. We demonstrate a new amplifier that miniaturizes and expands upon current technologies used in the most common environment for exploring single unit activity and deep brain structures in humans: the epilepsy monitoring and resection cases in research hospitals.
The goal of this poster is to characterize the new amplifier and demonstrate its capability at

enabling new avenues electrophysiology research. The poster demonstrates benchtop testing of frequency response, signal to noise ratio, compatibility with neural stimulators, and interface testing with upcoming electrode technology. Further, the poster is bolstered by in-human recordings demonstrating functionality of the device and recording capabilities that it enables.

Disclosures: **N.R. Halper:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. **C. Dryden:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. **M. Sorenson:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. **M. Gerhardt:** A. Employment/Salary (full or part-time):; Blackrock Microsystems. **F. Solzbacher:** A. Employment/Salary (full or part-time):; University of Utah. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Microsystems. **R. Franklin:** A. Employment/Salary (full or part-time):; Blackrock Microsystems.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.17/CC58

Topic: I.04. Physiological Methods

Support: Bertarelli Foundation
European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 665667
SNF Ambizione Fellowship No. 167912

Title: Biomimetic, multi-modal platform to validate soft neuroprosthetic technology

Authors: *G. SCHIAVONE[1], I. FURFARO[1], B. BARRA[3], F. FALLEGGER[1], J. BLOCH[5], G. COURTINE[2], M. CAPOGROSSO[4], S. P. LACOUR[1];
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Abstract: Soft bioelectronics leverages the mechanical compliance of soft materials to optimise the design of long-lasting electronic interfaces with biological tissue, for both sensing and modulation of neural activity. In the field of neuroengineering, numerous examples of soft neural interfaces have recently been reported in the scientific literature, indicating that mechanically compliant devices help mitigate foreign body reactions. Such shift towards soft technology, however, has not yet been complemented by a corresponding evolution in testing and validation of associated experimental protocols. Conventional methods are based on norms developed for clinical implants that become inadequate to the peculiar electromechanical characteristics of soft

bioelectronics. Materials and integrated interfaces now need to maintain electrical and electrochemical functionality while withstanding significant and complex strains.
We present here a biomimetic and multimodal in vitro platform that enables soft interfaces to be tested against simultaneous, anatomically relevant, mechanical and electrochemical stimuli in a temperature-controlled environment. As a case study, we have designed a system that mimics the mechanical environment of the cervical segments of the Non-Human Primate (NHP) spinal cord. We chose the neck region as this is the segment of the vertebral column that experiences the most demanding mechanical strain. Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) scans of a NHP were acquired to build models of the vertebrae and spinal cord, respectively, and prepare synthetic mock-ups. Replicas of the vertebrae were 3D-printed and assembled to form an artificial spine; a model of the spinal cord was reproduced using a moulded hydrogel enveloped in a thin silicone "dura mater". CT scans of the NHP were taken at rest and maximum strain postures in order to record 3D positions of the spine during physiological movements. The extracted coordinates were translated in spatial positions within a Stewart platform to replicate the natural displacements of the cervical segments. Cyclic actuation controlled via software automation was then applied to test the function and integrity of soft implants inserted "epidurally" in the spine model.
This multimodal and biomimetic approach to in vitro characterization enables both more pertinent evaluation of new neurotechnologies compared to standard protocols, and more efficient and faster development cycles compared to in vivo only testing.

Disclosures: **G. Schiavone:** None. **I. Furfaro:** None. **B. Barra:** None. **F. Fallegger:** None. **J. Bloch:** None. **G. Courtine:** None. **M. Capogrosso:** None. **S.P. Lacour:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.18/CC59

Topic: I.04. Physiological Methods

Support: HR0011-15-2-0030

Title: Evaluation of chronically implanted tissue-engineered-electronic-neural-interface (TEENI) for next-generation prosthetics

Authors: ***E. ATKINSON**[1], E. NUNAMAKER[1], A. K. GORMALEY[2], A. M. BRAKE[3], M. YUSUFALI[1], B. SPEARMAN[1], C. KULIASHA[1], A. FURNITUREWALLA[1], R. PARITOSH[1], S. MOBINI[1], C. SCHMIDT[4], J. W. JUDY[5], K. J. OTTO[1];
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Abstract: Advances in prosthetic limb development have allowed persons with amputations to improve their quality of life by allowing them to regain lost functions in a natural way that previous prosthetics have not been able to achieve. Stimulating neural tissue to elicit sensory precepts and recording electrical signals to control device motion can combine to produce amazing results for both patients and their families. While these devices hold much promise, their development still has several areas that require attention from the scientific, engineering, and medical communities. One of these areas that our group focuses on is a communication problem between tissue and computer systems. As prosthetic devices advance, the amount of information they need to function properly increases on average. While there likely exists some threshold of information bandwidth needed to provide baseline functionality, it makes rational sense that accessing more of the information contained in the neural tissue of a patient could provide higher-resolution sensory precepts and finer motor control with the maximum limit being that of a natural limb. Our approach to improving the available "natural limb" information that a prosthetic limb has access to involves interfacing with the remaining peripheral nerves that once projected to the missing limb.
The peripheral nervous system, unlike the central nervous system, exhibits a high propensity for regeneration. In the event of an amputation, doctors clinically manage the exposed nerve endings which can grow unguided causing painful neuromas. Typically, these nerve endings are placed into denervated, living muscle tissue such that they can have a target to reinnervate resulting in reduced neuroma formation. If these nerves were placed in a tissue-engineered scaffold surrounding a high-density, soft neural interface array and allowed to regenerate towards a distal target, it may be possible to achieve high information bandwidths into and out of the tissue. This study evaluates our device design referred to as a Tissue Engineered Electronic Nerve Interface (TEENI) using traditional cryosection-based immunohistochemistry, CLARITY cleared tissue with light-sheet imaging, and electrophysiological analysis. Each rat in the study had a small segment of the right sciatic removed and was then implanted with a TEENI device. Electrophysiology was recorded until the animal was euthanized and the tissue extracted for histological analysis. Preliminary results indicate successful recording of multiple action potentials per recording sites across multiple recording sites with histology revealing axons in close proximity to the device surface.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.19/CC60

Topic: I.04. Physiological Methods

Support: DARPA HR0011-15-2-0030

Title: Modeling the impact of size, shape, distance, and dielectric width on the recording performance of microelectrodes in peripheral nerves

Authors: A. FURNITUREWALLA[1], P. RUSTOGI[1], J. W. JUDY[1], ***E. E. PATRICK**[2]; [1]Univ. of Florida, Gainesville, FL; [2]Uniuniversity of Florida, Gainesville, FL

Abstract: Single action potentials (APs) from peripheral-nerve axons have been recorded intraneurally using a variety of microelectrode technologies. Since the ability to record single APs from many nerve fibers can help amputees control prostheses with higher precision, there is a drive to increase the count and density of microelectrodes in nerve fascicles. However, to design large-scale neural interfaces rationally, engineers need to be able to predict not only an optimal size and shape of the recording electrodes but also an optimal distribution and density of electrodes. This design-optimization problem is multifactorial since it depends on neural anatomy and morphology as well as nerve-fiber electrophysiology and the physics of volume conduction. Due to this complexity, quantitative rational design of microelectrode arrays for large-scale peripherals-nerve interfaces has yet to be performed. Fortunately, computational modeling provides a means to simplify and parameterize this complex design problem. We present physics-based computational modeling results that explore the dependence of important geometric design elements for planar microelectrode arrays fabricated on thin-film polymer dielectrics. We couple biophysical models of nerve fibers in NEURON with finite-element-method simulation of volume conduction in COMSOL. First, we explore the effect of electrode size and electrode-to-fiber separation on the amplitude of APs recorded from nerve fibers of various size. Results show that spatial averaging on a planar disc electrode greatly decreases signal amplitudes when the electrode-to-fiber distance is small and is worse for large electrodes. For example, an 8-um-diameter electrode would sense a signal amplitude that is twice that (or greater) of a 64-um-diameter electrode. Although this dependence falls off for greater electrode-fiber separations, the recorded signal approaches recording noise floors (~10 uV). Second, we explore the dependence of recording performance given a fixed electrode size and electrode-fiber separation and a variable width of surrounding dielectric. Although a smaller width of surrounding dielectric can increase interface density, simulations show that the amplitude of recorded APs is reduced. In addition, we use probability theory estimate the number of recordable fibers within a realistic population of nerve fibers. This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) HAPTIX program under the auspices of Drs. Doug Weber and Eric Van Gibson through the DARPA Contracts Management Office, Pacific Cooperative Agreement: No. HR0011-15-2-0030.

Disclosures: A. Furniturewalla: None. **P. Rustogi:** None. **J.W. Judy:** None. **E.E. Patrick:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

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Program #/Poster #: 522.20/CC61

Topic: I.04. Physiological Methods

Support: Bertarelli Foundation
Wyss Center
the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 665667

Title: MRI compatible soft microelectrode arrays for large scale recordings of brain surface activity

Authors: *F. FALLEGGER[1], G. SCHIAVONE[1], E. PIRONDINI[2], F. B. WAGNER[3], N. VACHICOURAS[1], G. COURTINE[3], J. BLOCH[2], S. P. LACOUR[1];
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Abstract: Neural implants such as electro-corticography devices (ECoGs) are used to identify the seizure foci in drug-resistant epilepsy, or eloquent brain regions in tumor resections. Current devices used in the clinic comprise a thick silicone shell (0.5-2 mm), which impedes conformal contact with the brain. The electrodes are thick metal disks embedded in silicone, millimeters in diameter and pitch, providing limited spatial resolution. Additionally, the presence of bulk metal is not compatible with magnetic resonance imaging (MRI), which prevents precise localization of the electrodes on the brain post-implantation and diagnosis of adverse post-operative effects. A technology enabling both increased conformability, spatial resolution and MRI compatibility is therefore highly desirable. Here, we present a soft microtechnology to fabricate MRI-compatible, conformable, large-scale neural interfaces that enable localized brain recordings. Soft microelectrode arrays are fabricated on 150 µm thick silicone layers using for the recording sites a composite of platinum particles dispersed in silicone, which creates a low-impedance soft contact to the neural tissue. The electrodes are accessed via a stretchable interconnect patterned in gold thin film. Soft µECoGs were used to record somatosensory evoked potentials on the cortex in a minipig model. The design versatility enables brain recordings with high spatial resolution and the conformal coating offers high signal-over-noise (SNR of 4-50). This technology is scalable and enables high channel counts and large area coverage (2-2400mm^2),

with a high yield (>95% functional contacts). Sample arrays laid on gel phantoms in saline solution have been tested for compatibility with a clinical 3 tesla MRI against artefact creation and induced radiofrequency (RF) heating. Compared to clinical arrays where the image artefact is extending several millimeters outside the device, the soft µECoGs do not produce artifacts larger than 0.6 mm. For the heating, after 15 minutes of a T2-weighted sequence, a maximum temperature increase of 0.54°C was recorded, well below the safety limit of 2°C.
With an outlook to adoption to the clinic, this technology could help mitigate the occurrence of adverse effects as well as provide improved diagnostic capabilities.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.21/CC62

Topic: I.04. Physiological Methods

Support: DARPA HR0011-15-2-0030
NIH 1R01NS111518-01

Title: Tissue-engineered electronic nerve interfaces (TEENI): Improved design, fabrication, and packaging using aggressive *in vitro* reactive-accelerated-aging reliability testing

Authors: C. A. KULIASHA, B. S. SPEARMAN, E. W. ATKINSON, K. J. OTTO, C. E. SCHMIDT, *J. W. JUDY;
Univ. of Florida, Gainesville, FL

Abstract: Peripheral neural interfaces (PNIs) for amputees should reliably capture the activity of motor neurons and stimulate activity in sensory neurons for the lifetime of the patient. Existing implants typically fail within months to a few short years. In order to achieve lasting success with PNIs, the must be engineered to properly interface with tissue and be rigorously tested to mitigate *in vivo* failure mechanisms. Our hybrid tissue-engineered electronic nerve interface (TEENI) consists of multi-electrode polyimide-based “threads” embedded into a biodegradable hydrogel composite scaffold that is wrapped in a bioresorbable small intestinal submucosa and sutured to the ends of a transected nerve. We have found that first-generation TEENI devices are susceptible to failure and can exhibit a consistent foreign-body response around the microelectrode threads. Herein, we report on design modifications to the TEENI microelectrodes and the use of aggressive *in vitro* reactive-accelerated aging (RAA) to facilitate rapid fabrication-process improvements of the device and the back-end packaging to better withstand the harsh implant environment. With RAA (7-days, 87 °C, 10 to 20 mM H_2O_2 in phosphate buffered

saline) we revealed that the epoxy-based polymeric packaging material used for first-generation TEENI implants was susceptible to oxidative degradation. Improved silicone encapsulation was found to be more resistant to this degradation and the resulting explants (3-months, rat sciatic nerve, $n = 3$) showed no signs of failure. First-generation TEENI devices also used an anisotropic-conductive-adhesive (ACA) connector technology to interface it with external electronics. Since the RAA testing revealed that ACA can rapidly fail due to moisture penetration into the package, we are pursuing improved connector strategies. We used RAA to improve the fabrication process to better resist polyimide-polyimide delamination, and we have successfully fabricated devices that can resist 3-days RAA (~3 months *in vivo*). We are now pursuing additional improvements to increase the duration of implant survival. Lastly, we are exploring the use of TEENI microelectrodes with reduced cross-sectional areas to reduce bending stiffness and foreign-body response. We are also using RAA to validate the robustness of the dimensionally reduced devices in preparation for *in vivo* implantation. This work was sponsored by the Defense Advanced Research Projects Agency (DARPA) Biological Technologies Office (BTO) HAPTIX program under the auspices of Drs. Doug Weber and Eric Van Gibson through the DARPA Contracts Management Office, Pacific Cooperative Agreement: No. HR0011-15-2-0030.

Disclosures: C.A. Kuliasha: None. **B.S. Spearman:** None. **E.W. Atkinson:** None. **K.J. Otto:** None. **C.E. Schmidt:** None. **J.W. Judy:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.22/CC63

Topic: I.04. Physiological Methods

Title: A multifunctional microelectrode array for long-term, high-resolution intracortical recordings

Authors: *J. M. HERRERA-MORALES[1], M. HEUSCHKEL[2], F. MOR[2], A. ROUX[2], A. WOODTLI[1], L. STOPPINI[2], J. DONOGHUE[1];
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Abstract: High resolution, long lasting sampling of neural, optical, chemical, or other activity in the nervous system for evolving applications such as brain-computer interfaces (BCIs) requires the long-term implantation of recording devices suitable for humans. Such sampling for humans BCIs has mainly involved one type of penetrating (intraparenchymal) array of multiple microelectrodes. These human BCI studies has provided proof of concept that cortical signals recorded with such technologies in people with paralysis can provide useful command signals for

several years, allowing people to control computers, assistive robotic limbs or even their own paralyzed limbs. However, current intracortical microelectrode arrays (MEAs) exhibit issues with long-term usability after implantation because of biotic and abiotic failures. Those abiotic in nature are due mainly to poor biostability of materials and related boundary layers in the harsh body environment. Additionally, current MEAs have complex manufacturing processes that are difficult to control and introduces sources of variability and device failure. Also, they are so far constrained in possible geometry configurations including the length, pitch, and shape of the probes due to manufacturing limitations. Finally, their cost is very high due to the intense technical effort required to manufacture them. Therefore, there is a need for a penetrating microelectrode array that can function for many years in the body and that can be (1) manufactured in a more automated and reliable manner and (2) provide greater flexibility of design (length, shape and pattern of electrodes) at a cost suitable for a device that can be commercialized for humans. The penetrating MEA presented in this exploratory study (the *Geneva Array*) addresses the above issues of long term biostability and design flexibility through recent advances in materials science and 3D microfabrication technology. This Geneva Array and consists of a multifunctional penetrating MEA laser fabricated from biostable bulk (glass) materials for insulation and support, as well as long term biostability, in conjunction with optical, electrochemically active materials for array functionalization, which is designed and produced to form highly reliable material interfaces between them. We will present results of electrical recordings of this novel MEA in 3D engineered neural tissue (ENT) made of neurons derived from human embryonic stem cells, as well as mechanical insertion tests in relevant tissues and mediums as a next step to in vivo implementation.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.23/CC64

Topic: I.04. Physiological Methods

Support: NSF REU 00052720
NSF REU 00057167

Title: Fully desktop fabricated, flexible electrocorticography electrode arrays

Authors: *A. D. TILLERY[1], J. HU[2], M. L. RYNES[2], P. DONALDSON[3], S. L. SWISHER[3], S. B. KODANDARAMAIAH[2];
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Engin., [3]Dept. of Electrical and Computer Engin., Univ. of Minnesota, Twin Cities, Minneapolis, MN

Abstract: Electrocorticography (ECoG) is a neural sensing modality that measures field potentials at the surface of the brain. The minimally invasive nature of ECoG allows long term implantation and facilitates high SNR signals as compared to scalp electroencephalogram (EEG) recordings. Recently, flexible ECoG electrode arrays have been developed that enable recording from large areas of the surface of the cortex by conforming to the 3D topology of the brain. However, current flexible ECoG arrays require MEMS processing and clean room operations, which greatly lower the accessibility of ECoG to unequipped neuroscience facilities. Here we demonstrate that readily available desktop tools - inkjet printers and nail salon ultraviolet (UV) curing lamps - can be harnessed to fabricate functional and flexible ECoG electrode arrays. Devices were fabricated by first printing silver nanoparticle (AgNP) ink, or PEDOT:PSS ink, onto a flexible polyethylene terephthalate (PET) film. A second print layer of SU-8 was applied to encapsulate the electrode leads, followed by curing under a UV lamp. Using this process, we have realized a fully functioning, 9-channel flexible ECoG sensor with a minimum print feature size of less than 100 μm, interelectrode pitch of 400 μm, and an electrode contact area of 0.01 mm^2. Following five-day submergence in 1x PBS, flexible arrays yielded impedances of 0.876 - 3.11 kΩ at 1 kHz. *In vivo* testing revealed electrode impedances in the range of 2.42 - 3.11 kΩ at 0.1 to 500 Hz and successful capturing of surface field potentials in anesthetized mice. We are working towards multilayered printing and streamlining the fabrication process so that it can be robustly applied in any neuroscience laboratory. We expect that this novel approach will facilitate high-level customization, accessibility, and rapid prototyping of ECoG sensors that can promote new kinds of experiments in neuroscience.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.24/CC65

Topic: I.04. Physiological Methods

Title: Separation of drug effects in human iPS cell-derived neurons using MEA system

Authors: Y. ISHIBASHI, M. SHIMIZU, S. TAKAHASHI, R. YOKOI, N. MATSUDA, A. ODAWARA, ***I. SUZUKI**;
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Abstract: In vitro human iPSC-derived neurons are expected to be applied to toxicity evaluations in nonclinical studies and drug screening. Microelectrode array (MEA) measurement system is suitable to evaluate the neuronal electrophysiological responses to drugs. We have previously reported the electrophysiological responses to several convulsive compounds using MEA in cultured hiPSC-derived neurons. (Elixirgen, LLC). In this study, we evaluated the responses to convulsants and anti-epilepsy drugs (AEDs) more than 15 compounds having different mechanism of actions in cultured hiPSC-derived neurons (Elixirgen, inc.). Among the 80 parameters, we identified a set of parameters that could separate the mechanism of action of the drug. Drug effects acting on GABA, Glycine, Glutamate, Dopamine, 5HT, Muscarinic receptors and Na channel, etc. were separated by principal component analysis and clustering analysis using identified parameters. It was suggested that spike data obtained by MEA measurement in cultured human iPS cell-derived neurons contained information on the efficacy of drugs having different mechanisms of action. Our analysis method of MEA data can be applied to elucidation of the mechanism of action of drugs, safety assessments of new drugs and screening.

Disclosures: I. Suzuki: None. **Y. Ishibashi:** None. **A. Odawara:** None. **N. Matsuda:** None. **R. Yokoi:** None. **M. Shimizu:** None. **S. Takahashi:** None.

Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.25/CC66

Topic: I.04. Physiological Methods

Support: Galvani Bioelectronics
DARPA ElectRx grant (N66001-16-2-4066)

Title: Extracellular recordings of peripheral nerve compound action potentials and consecutive-trace bioimpedance measurements

Authors: *T. M. SMITH[1], C. A. R. CHAPMAN[2], J. AVERY[2], N. THOMPSON[1], I. TAROTIN[1], M. KELLY[3], D. GOODWIN[4], K. ARISTOVICH[1], J. PERKINS[5], D. CHEW[6], D. HOLDER[1];
[1]Univ. Col. London, London, United Kingdom; [2]Imperial Col. London, London, United Kingdom; [3]Univ. of Newcastle, Newcastle, United Kingdom; [4]Royal Vet. Col., London, United Kingdom; [5]Royal Vet. Col., Potters Bar, United Kingdom; [6]Galvani Bioelectronics, Stevenage, United Kingdom

Abstract: In the peripheral nervous system, the complex organisation and heterogeneity of nerve fibres make the development of non-invasive imaging challenging and this limits the efficacy of

therapeutic interventions. Therefore, a technique to non-invasively image the neural activity of specific fibre types, especially unmyelinated fibres, is required to improve therapeutic efficacy. This research aims to develop a robust method, that is non-invasive to the nervous tissue, for recording neural activity from unmyelinated crustacean nerve fibres using bioimpedance. The Animal Welfare Act protects animals in the U.K. and suffering was minimised. Firstly, to ensure the validity of the model, the crustacean nerve model, fibre size and conduction velocity was characterised. Staining revealed that all fascicles showed a similar distribution of diameters with: 48% < 5 μm; 42% 5 - 13 μm and 10% > 13 μm (n = 3 crabs, 4 front and 4 rear leg nerves each). Then, hook electrodes were used to deliver a monophasic pulse to activate nerve fibres and the resulting compound action potential (CAP) was recorded and this revealed three distinct peaks at latencies of 2.83, 5.49, and 9.09 ms, corresponding to conduction velocities of 1.8, 1.05, and 0.61 m/s. These conduction velocities, reinforced by the histological fibre size distributions, strongly suggest these nerve fibres are a relevant model of unmyelinated C-fibres. To record bioimpedance changes due to the CAP, a 10 μA electrical impedance (EI) current was injected at 225 Hz between two electrodes, spaced 4 mm apart, 8mm from the supra-threshold neuronal stimulation. With the constant current sine wave applied at a frequency of 225 Hz and a novel randomised phase summation subtraction paradigm, a bioimpedance change of -0.377% ±0.072 (n = 4 crabs) and a maximal SNR of 13.2 ±4.3 were recorded, which was far greater than at 625, 825, 1000, 3000, 5000, 7000 Hz (n = 4 crabs at each frequency). The bioimpedance change became positive at 625 and 825 Hz. Using 225 Hz and 4 mm between electrodes resulted in bioimpedance changes up to a maximum distance of 56 mm away from the onset of the CAP (n = 5 crabs at 8, 20, 32, 44 and 56 mm), with a non-statistically significant change being recorded at 100 mm as the bioimpedance signal was -0.05 ±0.04 (n = 3 crabs at 100 mm). Together, these results indicate that, using the Crab peripheral nerve as a model of C-fibers, the optimal parameters for bioimpedance measurements are 225 Hz, with electrodes 4 mm apart, at a distance of 20 mm from the onset of activity. However, at longer distances from the onset of activity, the SNR of the bioimpedance change is not significant from noise, whereas the extracellularly recorded CAP is.

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Poster

522. Techniques: Microelectrodes II

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 522.26/CC67

Topic: I.04. Physiological Methods

Title: A fully transparent, flexible μECoG array based on highly conductive and anti-reflective PEDOT:PSS-ITO-Ag-ITO thin films

Authors: *W. YANG, Q. H. FAN, W. LI;
Electrical and Computer Engin. Dept., Michigan State Univ., East Lansing, MI

Abstract: Integrative neural interfaces combine neurophysiology and optogenetics with neural imaging, providing numerous opportunities for neuroscientists to study the structure, function, and diseases in neural circuits. Such a comprehensive interface demands miniature electrode arrays that are highly transparent, mechanically flexible, and biocompatible. Compared to implanted electrodes, microscale electrocorticogram (μECoG) arrays are less invasive, therefore reducing the risk of stroke, hemorrhage, and infection. Conventional transparent μECoG electrodes made of a single material, such as indium tin oxide (ITO), ultrathin metals, graphene and poly-(3, 4-ethylenedioxythiophene)/poly(styrenesulfonate) (PEDOT:PSS), have limitations and hardly possess the desired combination of broadband transmittance, low electrical resistivity, mechanical flexibility, and biocompatibility. Herein, we designed and constructed an ultra-flexible, highly conductive, fully transparent, and peak-transmittance-tunable μECoG array using a PEDOT:PSS-ITO-Ag-ITO multilayer structure on a thin Parylene C substrate. Each array consisted of 32 transparent microelectrodes distributed uniformly and divided equally into two 2.5 mm× 2.5 mm panels. To fabricate the μECoG array, 10 μm Parylene C was deposited on a silicon wafer. ITO-Ag-ITO thin films were deposited using magnetron sputtering and were then patterned using a lift-off process. The thicknesses of the individual layers were optimized using admittance loci to maximize the optical transmittance at a targeted wavelength. Next, a 2 μm Parylene C was deposited on the substrate as an insulating layer, and the contact pads and microelectrode areas were subsequently exposed to air by dry etching. Finally, 500 nm copper was sputtered on the contact pads and PEDOT:PSS was spun on the recording sites. The transmittance of the PEDOT:PSS-ITO-Ag-ITO assembly under the targeted wavelength on the Parylene C substrate was ~7% higher than that of a single ITO layer of the equivalent thickness. The impedance of the microelectrodes at 1 kHz was ~8 kΩ, suitable for electrophysiology recording. Microelectrodes based on PEDOT:PSS-ITO-Ag-ITO also showed an enhanced signal-to-noise ratio compared with the plain ITO electrodes. *In vivo* recording from the primary visual cortex of anesthetized rats validated the efficacy of the transparent electrodes for electrical detection of ECoG activity in living brain tissues.

Disclosures: **W. Yang:** None. **Q.H. Fan:** None. **W. Li:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.01/CC68

Topic: I.06. Computation/ Modeling/ and Simulation

Support: AFOSR FA9550-18-1-0054
Canada Research Chairs Program 950-231659
NSERC RGPIN-2016-05352

Title: Early recurrence enables figure border ownership

Authors: P. MEHRANI, *J. K. TSOTSOS;
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Abstract: Rubin's face-vase illusion demonstrates how one can switch between two different interpretations depending on how the figure outlines are assigned [1]. This border ownership assignment is an important step in the perception of forms. Zhou et al. [2] found neurons in the visual cortex whose responses not only depend on the local features present in their classical receptive fields, but also on their contextual information. Various models proposed that feedback from higher ventral areas or lateral connections could provide the required contextual information. While some [3, 4, 5] ruled out the plausibility of models exclusively based on lateral connections, further evidence [6] suggests that ventral feedback even from V4 is not fast enough to provide context to border ownership neurons in V1 and V2. Therefore, the border ownership assignment mechanism in the brain remains unclear. We tested, with computational simulations, the hypothesis that the dorsal stream provides the global information to border ownership cells in the ventral stream. A novelty of our model is its combination of global and local context by incorporating dorsal early recurrence and ventral lateral modulations. Computationally fast dorsal cells with large receptive fields provide global context while ventral lateral modulations present local context and enforce collinearity for border ownership. Our simulation experiments show that our model border ownership neurons exhibit the appropriately different responses to figures on either side of the border and are invariant to position, size, and solid/outlined figures as observed in biological cells. Furthermore, our model cells assign borders to the occluding figure along the occlusion boundaries of overlapping shapes. Interestingly, testing with Pokemon figures, our cells respond to the illusory occluding shape. In conclusion, neurophysiological evidence regarding latencies together with our simulations support the hypothesis that dorsal recurrent and ventral lateral modulations cooperatively enable border ownership assignment.

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[6] Yau, J. M., Pasupathy, A., Brincat, S. L., Connor, C. E. (2012). *Cerebral Cortex*, *23*(1), 198-209.

Disclosures: **P. Mehrani:** None. **J.K. Tsotsos:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.02/CC69

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF CAREER 0952686

Title: Triplet motifs sustain activity in sparse recurrent networks

Authors: ***Y. ZHU**, K. R. BOJANEK, J. N. MACLEAN;
Neurobio., The Univ. of Chicago, Chicago, IL

Abstract: Activity propagation is the most basic function that arises from the structure of neocortex. However, synapses are weak and connections are both sparse and recurrent, making it unclear how local connectivity supports stable spike propagation in local circuits. Several lines of evidence suggest that higher order network interactions may be instrumental for spike propagation. Synaptic connectivity displays a prevalence of local neuronal cliques and motifs, and propagating activity in vivo displays elevated clustering dominated by specific triplet motifs. Here we algorithmically build and analyze spiking neural network (SNN) models to explore the role of higher-order interactions in activity propagation. These models are recurrent and sparsely-connected with conductance-based synapses and are comprised of excitatory and inhibitory adaptive exponential leaky integrate-and-fire (AdEx) neurons. Network topology parameters are optimized using grid search bounded by experimental measurements and result in naturalistic activity in our simulations - that is, networks display asynchronous, low-rate, and critical spiking regimes. We find that simulations of the same topological SNN can either spontaneously stop (truncate) or show sustained spike propagation on different runs despite identical initial conditions in the simulations. Using graph theoretic and probabilistic methods, we find that sustained activity requires cyclic higher-order coordination amongst excitatory neurons. In particular, the network cycles through epochs dominated in turn by three types of triangle motifs. The fan-in triangle motif is predominant, consistent with the need for nodes to integrate information from multiple sources. The network then cycles through middleman, a hallmark of recurrence, and fan-out triangles which distribute information. When a network fails to engage this dynamical regime, activity is not sustained and truncates. We also find that for each network, there exists a unique linear relationship between the probabilities of each of the three motif types being most dominant in the network at any point in time. Successful runs occupy a highly restricted range of values on this line of probabilities. Our results provide a mechanistic account and possible explanation for the widespread findings of clustered activity as well as synaptic connectivity in local neuronal circuits.

Disclosures: **Y. Zhu:** None. **K.R. Bojanek:** None. **J.N. MacLean:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.03/CC70

Topic: I.06. Computation/ Modeling/ and Simulation

Support: KAKENHI 18H05213
KAKENHI 19H04994

Title: Extended associative memory by inhibitory modulation

Authors: *T. HAGA[1], T. FUKAI[2];
[1]Ctr. for Brain Sci., RIKEN, Wako, Japan; [2]Okinawa Inst. of Sci. and Technol. Grad. Univ., Onna-Son, Japan

Abstract: Associative memory is one of fundamental functions in the brain. To model this function, attractor network models based on excitatory Hebbian learning, typically represented by Hopfield model (Hopfield, 1982), has been used. Hopfield model learns memory patterns as attractors through Hebbian learning within each pattern, which enables memory retrieval from incomplete stimulus (pattern completion). Griniasty, Tsodyks and Amit (1993) extended Hopfield model by adding inter-stimulus Hebbian learning terms, which makes the attractor patterns correlated to each other even if memory patterns (stimulus) are mutually uncorrelated. This model can explain experimental observations of correlation between neural representations for associated memory items. As described above, Hebbian learning of excitatory synapses has been extensively studied. However, although recent experimental findings strongly suggest the computational importance of inhibitory learning in associative memory (Barron et al., 2017), the contribution of inhibitory circuits and plasticity to associative memory has not been theoretically understood. Here, we report that introducing anti-Hebbian learning to Griniasty-Tsodyks-Amit model, which can be implemented by pattern-specific local inhibition, gives previously unknown attractor states. In this state, the range of temporal association between memory items significantly extends. In other words, an attractor is correlated with a larger number of memory patterns and attractors are correlated more in this state than the original model. Furthermore, this extension is accompanied by the increase of susceptibility of attractors to external inputs, that is, an attractor pattern in this state can be easily shifted to other patterns by much weaker inputs than the attractors in the original model. We show that this change of attractor states can be continuously controlled by changing the ratio of local/global inhibition in a neural network, and those inhibition weights can be optimized by the inhibitory plasticity rule for excitation-inhibition balance (Vogels et al., 2011). Functionally, this model can be related to cholinergic modulation of inhibitory circuits and uncertainty. Furthermore, with inhomogeneous association

between memory items, this model can perform multi-resolution grouping of memory items based on the associative network structure. In sum, our model suggests an essential role of inhibitory modulation and plasticity in associative memory.

Disclosures: T. Haga: None. **T. Fukai:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

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Program #/Poster #: 523.04/CC71

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Simons Foundation, Collaborative Grants for Mathematicians
SUNY New Paltz Provost Office, Research and Creative Projects Award
SUNY New Paltz Research, Scholarship and Creative Activities, AYURE

Title: Predicting dynamics from connectivity patterns in networks of canonical neural oscillators

Authors: *A. RADULESCU, S. EVANS;
Mathematics, State Univ. of New York at New Paltz, New Paltz, NY

Abstract: A point of great interest in computational neuroscience has been to explain how the hardwired structure of a network (such as the brain) affects its temporal function. The question has crucial applications and has earned its own subfield of study (currently known as *dynomics*). However, the task of translating connectivity patterns to ensemble temporal behavior presents the difficulty of simultaneously addressing the complexity of the graph and the richness of the coupled dynamics. This may be computationally intractable, even for relatively small network sizes and for reduced models of node-wise neural dynamics. To shed light on this relationship, a recent strategy has been to investigate it in basic theoretical models, where one may more easily identify and pair specific structural patterns to their effects on dynamics. For example, in threshold linear networks (Curto and Morrison, 2016), complex ensemble behavior emerges from simple, almost linear node-wise dynamics. This makes it feasible to identify relationships between specific configurations and corresponding dynamic patterns. While this represents remarkable progress, it is important to establish whether this type of predictive analysis can be applied to other classes of models.
We use quadratic maps as a canonical way to model a neural response function in each of the network nodes. In this case, one can conveniently use the system's asymptotic (Julia and Mandelbrot) sets to calculate, visualize and interpret the long-term behavior of the system (in both phase and parameter spaces, with the network structure acting as a bifurcation parameter). The advantage is that of using clear topological markers (e.g., connectedness of a set) as the signature for the global dynamics of the system, amenable for prediction and classification. We

present our first robust classifications of ensemble behavior based entirely on the network architecture, independently on the node-wise dynamics.
We compare our results with those in other simplified models, proposing that some aspects may be universal to nonlinear networks, and hence could be further applied to physiological models with more complex dynamics. We discuss how our results compare with the classification of attractor sets in threshold linear networks, and with synchronization and clustering behavior in inhibitory Hodgkin-Huxley neuronal networks (Golomb and Rinzel, 1994). In each case, we use the appropriate measures of synchronization and stability to assess and classify long-term dynamics; then we check if there is any overlap (*universality*) in these classifications.

Disclosures: A. Radulescu: None. **S. Evans:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

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Program #/Poster #: 523.05/CC72

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF Grant DMS-1363161

Title: Correlations, population dynamics, and structural connectivity

Authors: *S. SARAF, L.-S. YOUNG;
New York Univ., New York, NY

Abstract: This is a theoretical study of correlations in spiking activity between neuronal populations. We develop a metric for quantifying brief-timescale spiking correlations, designed to capture the population firing structure without regard for individual neuron spikes. We show that due to the random behavior of single neurons, a population-level metric is more robust. In addition, the correlation is subject to an intrinsic optimal delay between source firing and target response. This method can be used to shed light on the transference of gamma rhythms between populations in a multi-component network. Because of hypotheses of the importance of gamma-band activity in information transfer, stimulus representation, and cortical state, quantifying the similarity between rhythmic firing of two populations would be a logical step in studying communication within the brain and neurological disorders that manifest as abnormal firing patterns.

Disclosures: S. Saraf: None. **L. Young:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.06/CC73

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF award 1718991
Intel INRC
NIH 1R01EB026955-01

Title: Robustly encoding multiple variables on smooth manifolds in a spiking model of hippocampus

Authors: *E. P. FRADY[1], F. T. SOMMER[2];
[1]UC Berkeley, Berkeley, CA; [2]Univ. California, Helen Wills Neurosci Inst., Helen Wills Neurosci. Inst., Berkeley, CA

Abstract: It is often argued that sensory areas extract behaviorally meaningful variables, often organized on smooth manifolds. Here we ask how combinations of such variables, once extracted, should be encoded to enable the brain to carry out critical computations for memory, planning and action. A useful encoding scheme has to fulfill two fundamental requirements: (1) Distinguishability: Points far apart on a manifold, should be encoded by dissimilar (independent or orthogonal) "indexing" patterns so that the probability of confusion is low. (2) Smoothness: Points close to each other should be encoded by similar patterns such that the code is noise tolerant and points can be represented by interpolation of neighbors. Some evidence that population codes in the brain fulfill these properties has been recently provided (Stringer⋯Carandini, Harris, 2018). Here we propose a normative encoding model with properties (1)-(2), leveraging timing of individual spikes. Our approach is based on complex-valued connectionist models (Plate, 1993), and recent theoretical results on how dynamics in complex state spaces can be mapped onto the dynamics of spiking neural networks (complex phase represented by spike-timing; Frady & Sommer, 2019). Our coding model "tiles" a manifold such that each location is represented by a unique neural activity vector that can be used as an index (1), but also in a way that transitions between neighboring tiles are smooth (2). As we show, this is accomplished naturally in the complex domain, with the sinc function as a universal kernel. Our approach is demonstrated in a model of hippocampus neurons that encode location and heading direction. The behavioral variables are organized onto smooth manifolds with appropriate topology: linear topology for location, and ring topology for heading direction. The coding model combines these individual representations of location and heading-direction into a representation of their conjunction, satisfying conditions (1) and (2). The resulting representation enables computations that are essential for navigation, such as the coordinate

transform from an egocentric to allocentric reference frame. Our model helps to explain recent observations of conjunctional receptive fields (Hoydal⋯Moser, 2019), and how to relate computation with manifold structure observed in neural recordings (Low⋯Tank, 2018). Specifically, the model suggests the intrinsic structure of neural recordings is influenced by: (i) manifold dimensionality (number of variables), (ii) manifold smoothness and resolution (number of tiles), and (iii) redundant neural dimensions for robustness.

Disclosures: E.P. Frady: None. **F.T. Sommer:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.07/CC74

Topic: I.06. Computation/ Modeling/ and Simulation

CCDC Army Research Laboratory contract W911NF-17-2-0158

Title: Cognitive chimera and synchrony states in human brain networks

Authors: *K. BANSAL[1,2], J. O. GARCIA[2], J. M. VETTEL[3];
[1]Columbia Univ., New York, NY; [3]Future Soldier Technologies Div., [2]CCDC Army Res. Lab., Aberdeen Proving Ground, MD

Abstract: The human brain is a complex dynamical system, and it functions through the emergence of spatiotemporal patterns of coherent and incoherent activity as regional neuronal populations interact. To support cognitive processing, these patterns of activity need to balance successful segregation of information for localized processing while also maintaining efficient integration of information for global coordination. As different regions dynamically interact to perform cognitive tasks, variable patterns of synchrony can be observed, including chimera states with separate domains of synchronized and de-synchronized dynamics and metastable states with intermittent synchrony and desynchrony. We propose that the spatial patterning of these synchrony states, within the regions of the brain, plays a fundamental role in guiding the emergence of human cognitive abilities and individual variability. A chimera-based framework allows us to analyze this patterning and understand its implications for cognition. In our recent paper (Bansal et al. 2019, Sci Adv), we used this framework to study individual differences in structurally-constrained computational models. Our results identified that different cognitive networks within the human brain show different levels of subject-specific and region-specific structural variability, accounting for the functional role they serve. Here, we extend this work on structural models to study functional neuroimaging data. We hypothesized that the evolution of chimera and synchrony patterns in functional brain dynamics will capture variability between tasks. More specifically, patterns would capture the segregation or integration of cognitive

systems specific to the regions previously associated with task dynamics. Our results demonstrate that the spatial patterning of synchrony states not only shows task-dependent changes, but it can be used to dissociate individual variability in task performance.

Disclosures: **K. Bansal:** None. **J.O. Garcia:** None. **J.M. Vettel:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.08/CC75

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Department of Biotechnology , Ministry of Science and Technology (DBT) - BIO/17-18/303/DBTX/SRIN

Title: Do tuned responses in cerebral microvessels imply lateral interactions among vessels? A computational study

Authors: *B. S. KUMAR[1], N. MAYAKKANNAN[1], **S. V. CHAKRAVARTHY**[1], P. KARA[2]; [1]Dept. of Biotech., Indian Inst. of Technology, Madras (IITM), Chennai, India; [2]Univ. of Minnesota, Minneapolis, MN

Abstract: Studies on cat's visual cortex (O'Herron et al 2016) have shown the existence of orientation and direction sensitivity in cerebral microvessels. In some cases, interestingly, orientation tuning of the vessels is quite different from the orientation tuning of its neural neighborhood. In order to account for this discrepancy, the authors of that study speculate that there could be propagation of dilatory signals from adjacent neural functional columns along vessel walls. We investigate this question using a computational model of neurovascular network and explore the right pattern of lateral interactions among the vessels that can account for the orientation tuning of the cerebral vessels and the neurons they perfuse. To this end, we use a biologically plausible self-organizing network known as Gain Controlled Adaptive Laterally connected network (GCAL) to model orientation and direction sensitivity in visual cortical neurons. This neural network is bidirectionally connected with a network of vascular units. Each unit of the vascular network integrates vasodilatory signals from the neural network through weighted connections, while each neuron integrates the flux of metabolic signals from the vascular network. The vessels are assumed to have circularly symmetric, center-surround type of lateral interactions. Three alternative forms of lateral interactions among the vessel units are considered. (1) No lateral connection (2) Excitatory center and inhibitory surround (3) Inhibitory center and excitatory surround. The afferent and lateral connections of neural and vascular layers are trained using Hebbian learning for the above three cases of lateral connectivity in the vessels. The performance of the neural and vascular layer is compared with the experimental

observations (O'Herron et.al 2016) and the architecture of vascular network that best matches with the experimental observation is selected. The performance is evaluated in terms of orientation selectivity index (OSI) and directionality index (DI). It is observed that when the vessels have a lateral interaction comprising of inhibitory center and/or excitatory surround, the performance of the proposed neuro-vascular system closely matches the experimental observations. The model suggests that the vascular network has active signaling within itself in an OFF-center, ON-surround fashion. These model predictions are consistent with previously reviewed evidence for existence of dynamic signaling within microvascular beds (Secomb and Pries 2002; Pradhan and Chakravarthy 2011).

Disclosures: B.S. Kumar: None. **N. Mayakkannan:** A. Employment/Salary (full or part-time):; Department of Biotechnology , Ministry of Science and Technology (DBT) - BIO/17-18/303/DBTX/SRIN. **S.V. Chakravarthy:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Department of Biotechnology , Ministry of Science and Technology (DBT) - BIO/17-18/303/DBTX/SRIN. **P. Kara:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

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Program #/Poster #: 523.09/CC76

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSFC 31650110468

Title: Synaptic plasticity rules for maintenance of spatial working memory

Authors: *J. GU, **S. LIM**;
Ctr. of Neural Sci., New York Univ. Shanghai, Shanghai, China

Abstract: Persistent activity that lasts long after the stimulus offset has been thought to underlie working memory. Interactions between neurons in recurrent networks were suggested to support such a persistent activity beyond the scale of membrane time constant. However, with perturbations in network connectivity, memory performance can be impaired. Here, we explored synaptic plasticity rules which enable to recover the ability to maintain persistent activity in particular for spatial working memory. Previously, Xie and Seung (1999) [1] showed that an unsupervised learning rule that penalizes the sum of squared changes (time-derivative) of activities can recover memory performance to maintain a graded persistent activity. We found that the network with such a plasticity rule only maintains spatially uniform patterns and the network for spatial working memory requires an additional factor that reflects the spatial pattern such as a plasticity rule that penalizes time-derivatives weighted by their activity. Furthermore, we found a condition under which a spike-time dependent plasticity rule can be approximated by

this rate-dependent synaptic plasticity rule and demonstrated its performance in a spiking neural network. [1] Xie and Seung (1999) Spike-based learning rules and stabilization of persistent neural activity, NIPS

Disclosures: J. Gu: None. **S. Lim:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.10/CC77

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Structural functional relationships in the human brain networks

Authors: *F. ZAMANI ESFAHLANI[1], J. FASKOWITZ[1], B. MIŠIĆ[2], R. BETZEL[1];
[1]Psychological and Brain Sci., Indiana Univ. at Bloomington, Bloomington, IN; [2]McConnell Brain Imaging Centre, Montréal Neurolog. Inst., McGill Univ., Montréal, QC, Canada

Abstract: Nervous systems are complex networks comprised of spatially-distributed regions. These regions are linked to one another by structural and functional connections that represent interregional white-matter fiber pathways and pairwise statistical relationships between regional activity, respectively. It is widely understood that functional connectivity (FC) reflects the outcome of an ongoing dynamical process and is constrained by the underlying structural connectivity (SC). However, the precise mapping of SC to FC is poorly understood, especially at the level of individual brain regions. Moreover, little is known about how this relationship is modified across the lifespan as the brain develops, matures, and enters senescence.
To better understand the relationship between SC, FC, age, and location in the brain, we analyzed neuroimaging data from the NKI-Rockland sample. This publicly available dataset includes structural, diffusion, and resting state-functional MRI data for >1000 subjects and includes ages ranging from 6 to 85 years. We preprocessed and used these data to generate structural and functional networks for a final sample of 587 subjects.
For each subject and for every pair of brain regions, we calculated 22 network measures that quantified the ease of information flow under different communication policies. These policies ranged from “communication-along-shortest-paths” (path length) to “communication-along-paths-of-all-lengths” (communicability). Next, we combined these network measures as predictors in a multilinear regression model to predict the strength of the FC from one region to all other regions. The goodness of fit between observed and predicted FC was quantified using the coefficient of determination measure, R-square. Finally, to assess age-related changes in model fitness, we computed the correlation of the R^2 value with age for every brain region.
In general, we found that R^2 was higher in visual networks ('VisPeri', 'VisCent': R^2= 0.33, 0.32) suggesting their higher correspondence in SC and FC and lowest in a sub-component of the

control network ("ControlA": R^2=0.2). Interestingly, we found that model fitness within both visual sub-networks as negatively associated with the subject's age (r=-0.37, -0.28, p<0.001). Our findings suggest that the relationship between SC and FC is not uniformly distributed in the brain. Rather, there are brain areas such as primary sensory cortices that their FC patterns are more likely to be explained in terms of their SC properties compared to the transmodal areas. The difference of SC-FC mapping in primary sensory areas with transmodal areas needs to be further investigated.

Disclosures: F. Zamani Esfahlani: None. **J. Faskowitz:** None. **B. Mišić:** None. **R. Betzel:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.11/CC78

Topic: I.06. Computation/ Modeling/ and Simulation

Support: CFREF-HBHL
NSERC

Title: The organization of functional connections without direct structural links

Authors: *Z.-Q. LIU[1], R. F. BETZEL[2], B. MISIC[1];
[1]McConnell Brain Imaging Centre, Montreal Neurolog. Institute, McGill Univ., Montreal, QC, Canada; [2]Dept. of Psychological and Brain Sci., Indiana Univ., Bloomington, IN

Abstract: INTRODUCTION
Human cognition is supported by a networked system of interacting brain areas operating on different hierarchies. Functional connections (FC) are thought to be emergent from and soft-constrained by the underlying sparse structural connections (SC). FCs without SC vastly outnumber those with direct SC links, but their organization is not completely understood. This study aims to describe the organizational principles of those structurally-unconnected FCs by studying their 1) spatial distribution, 2) topological arrangement, and 3) correspondence to cortical processing hierarchies.
METHODS
MRI-derived structural connectivity and functional time series data of 66 subjects are used to construct 1000-by-1000 group consensus SC and FC matrices. FCs were first binned by Euclidean distance. Within each distance bin, FCs with no direct SC link were then expressed as a z-score relative to the distribution of FCs with a direct SC link. This method uses the well-known relationship between spatial proximity and connection strength to identify FCs that are stronger than would be expected on the basis of their length. A robust z-score value is then

estimated by averaging over a spectrum of bin sizes. We then study the topological and hierarchical organization of the resulting z-scored FC ('ZFC') matrix.
RESULTS
The ZFC values represent an intuitive depiction of FC that accounts for the spatial embedding between brain regions. We find that a large proportion of FCs with no direct SC link are significantly stronger than expected on the basis of their length and display greater variability. Interestingly, transmodal areas at the top of a putative sensory-fugal hierarchy tend to participate in a disproportionately large number of unexpectedly strong (i.e. high-ZFC) connections. Finally, the ZFC matrix displays a rich modular structure with high ZFC values residing within resting-state networks, suggesting that this intrinsic network architecture is driven by functional interactions that transcend spatial embedding.
CONCLUSIONS
Our work examines organizational principles of structural-unconnected FCs, emphasizing the importance of studying the subset of FC without direct structural links. We demonstrate a distance-corrected baseline method that can be adopted for robust SC-FC relationship modelling, and shows a correspondence with functional hierarchies of the brain.

Disclosures: Z. Liu: None. **R.F. Betzel:** None. **B. Misic:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.12/DD1

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF Grant DMS-1361145
Washington Research Fund

Title: Systematic computational ablation for identification of oxygen sensation functional pathways in *caenorhabditis elegans*

Authors: *J. KIM[1], E. SHLIZERMAN[2];
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Abstract: The nematode Caenorhabditis elegans (C. elegans) is known to perform aerotaxis, behavior in which locomotion is modulated according to the composition of air in the environment. Sensory neurons related to O2 aerotaxis have been proposed through experimental research. In particular, it was shown that the sensory AQR neuron, located in anterior body, is a possible trigger for changing O2 level. Here we utilize a recently introduced C. elegans neuromechanical model, which emulates the full nervous system response to stimuli, and

simulate muscles commands and body postures. We employ the model to investigate behavioral responses to O2 and identify associated functional pathways. Our approach is to introduce spatial gradients which incorporate information about stimulation into neurons depending on the body position. We validate the model by placing an AQR gradient as an obstacle for forward locomotion and observe a steering away response from the gradient, as observed in experiments. Consequently, we propose a computational ablation approach for examination and testing of the effective functionality of AQR's sensorimotor neural pathways.
In particular, we propose a Combinatorial Neighbor Ablation (CNA), in which for a given set of neurons, all possible combinations of connected neighboring neurons are enlisted and ablation is performed for each combination. Application of CNA to the AQR neuron identifies a command neuron, PVPL and (PVPR, DVC) pair, that have the highest correlation with AQR induced O2 sensation, i.e., their ablation masks motor response when introduced with AQR gradient. Furthermore, to discover additional pathways that lie beyond neighbors of AQR, we perform Conditional Group Ablation (CGA) algorithm. CGA surveys and ablates each and every neuron in particular group (e.g. interneurons) given ablations of particular neurons. From CGA, we uncover additional functional pathways utilized by AQR, such as interneurons RIH and RIGR. With this study we show that C. elegans in-silico model in conjunction with spatial stimulation and systematic ablation can assist in identifying behavioral functional pathways and circuits, even in a complex model that incorporates connectomics, dynamics and body postures, exhibiting intricate behaviors such as aerotaxis.

Disclosures: J. Kim: None. **E. Shlizerman:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.13/DD2

Topic: I.06. Computation/ Modeling/ and Simulation

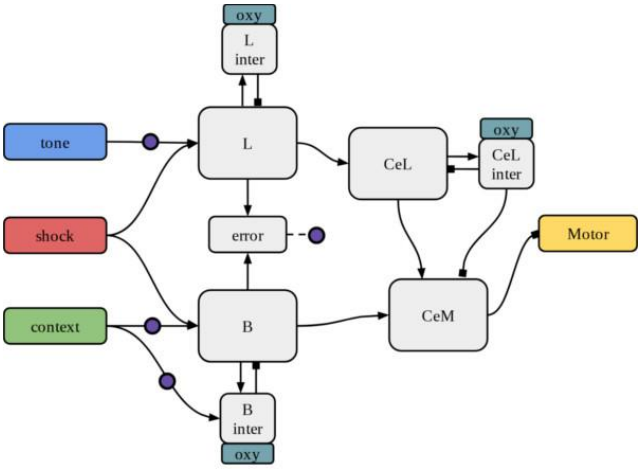
Support: GRS 122219

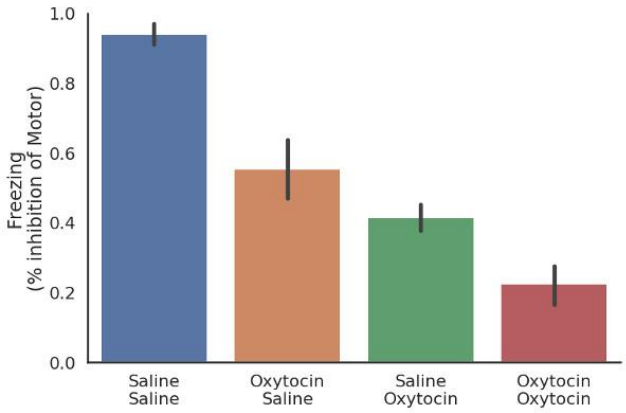
Title: A spiking neuron model of pharmacologically-biased fear conditioning in the amygdala

Authors: *P. DUGGINS[1], C. ELIASMITH[2];
[1]Univ. of Waterloo, Waterloo, ON, Canada; [2]Univ. Waterloo, Waterloo, ON, Canada

Abstract: Network models that reconstruct (a) the dynamics of individual neurons, (b) the anatomy of specific brain regions, and (c) the behaviors governed by these regions are important for understanding mental disorders and their pharmacological treatment. We present a spiking neuron model of the rat amygdala that undergoes fear conditioning, and is appropriately modulated by GABA agonists like oxytocin (OXY). The network includes neural populations for

the lateral (L), basal (B), central-lateral (CeL), and central-medial (CeM) amygdala; interneurons; inputs from cortex and hippocampus; and (Motor) output. The model is trained by pairing negative stimuli (footshocks) with neutral stimuli (auditory tones) within a prescribed context (conditioning cage). Prediction error signals drive associative learning of synaptic connection weights in L and B. Following an experimentally-vetted training regime, the model exhibits the fear response (freezing, via CeM inhibition of tonically driven Motor) to presentation of the conditioned tone or context. Furthermore, repeatedly presenting tones without shocks in a new context causes extinction of the fear response in that context, but not in others. To simulate the pharmacology of OXY, we excite L-, B-, and CeL-interneurons known to express the OXY receptor. Applying OXY during training and/or testing significantly impairs the model's fear responses (Figure 1, mean and 95% confidence intervals reported over n=10 simulated trials), consistent with the reduced freezing observed in rats injected with OXY or other GABA agonists (muscimol). These results demonstrate that the mechanisms underlying fear conditioning, including associative learning, extinction, and pharmacology, can be understood through the dynamic interactions between amygdala nuclei. Extensions to the model will allow targeted biophysical manipulations and anatomical reconstructions of human amygdala; experimental predictions made from this model may profitably inform human pharmacology and the treatment of conditions such as post-traumatic stress disorder.





Disclosures: **P. Duggins:** None. **C. Eliasmith:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.14/DD3

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Intel grant CG42647565

Title: Solving the exploitation vs exploration dilemma of reinforcement learning using a network of spiking neurons with reward-modulated STDP

Authors: *M. V. BAZHENOV[1], G. P. KRISHNAN[1], Y. SOKOLOV[1], N. IMAM[2];
[1]Univ. of California San Diego, La Jolla, CA; [2]Intel Corp., Santa Clara, CA

Abstract: One of the fundamental problems in reinforcement learning (RL) is the exploitation vs exploration dilemma. This dilemma can be observed in the multi-armed bandit task, a classic RL problem. Through continuous interaction with the environment, the agent has to learn a strategy to choose an optimal arm that maximizes the total expected reward. In this study, we considered a multilayer network model of spiking neurons that was capable of learning the unknown parameters of the Bernoulli bandits' reward distributions. Using reward-modulated spike timing-dependent plasticity (STDP) along with homeostatic mechanisms, the network was capable of learning the unknown information on a synaptic level and ultimately able to identify the arm with the highest reward. In this model, a switch from the mainly exploration phase to the mainly exploitation phase occurred when enough information about each arm had been gained. This phase switch was mediated by the homeostatic plasticity rules that operate to maintain a constant firing rate in the network by reducing synaptic weights to suboptimal arms. In addition, when reward distributions were allowed to vary throughout simulation, the intrinsic randomness of spiking neurons helped to increase performance by forcing the agent to explore the continually changing environment. We implemented this model on Intel's Loihi neuromorphic chip and demonstrated that it performs well with space and time limitations as compared to other existing methods. The study predicts the importance of homeostatic scaling for learning multiple reward distributions and, more importantly, for keeping the network in a state of high awareness, helping the network observe changes in the environment.

Disclosures: M.V. Bazhenov: None. **G.P. Krishnan:** None. **Y. Sokolov:** None. **N. Imam:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.15/DD4

Topic: I.06. Computation/ Modeling/ and Simulation

Support: DFG Collaboratory Research Center 1315

Title: Multistability in the global dynamic of inter-areal brain networks - A model comparison

Authors: *C. DIMULESCU, N. ROTH, K. OBERMAYER;
Technische Univ. Berlin, Berlin, Germany

Abstract: Computational modelling of the human brain has the potential of not only offering tremendous insight into its underlying functioning mechanisms, but also to provide a framework for testing and optimizing experimental protocols, in particular transcranial current stimulation, before delivering it to patients. The most powerful class of models revolves around the idea that the brain operates as a nonlinear dynamical system at the edge of criticality, which continually explores multiple functional states, only to collapse into a certain state given some task. In this context, it is important to have a thorough understanding of the system's dynamical landscape and the influence that each parameter has on it. In particular, we are interested in identifying the regions where the topology of the network supports multistability, meaning that the system can easily transition from one stable state to another. To this end, two models for the dynamic of individual nodes are employed in the current work. On the one hand we consider a computationally efficient, biophysically calibrated neural mass model [1], that supports various dynamical states, including low and high activity fixed points, bistability, and limit cycles. On the other hand, with the FitzHugh-Nagumo model we consider a much simpler dynamic, that phenomenologically still resembles the low and high fixed points, as well as a limit cycle. In a first step, the topology of the network is constrained based on healthy participant data from diffusion-tensor imaging, while resting-state functional resonance imaging is used to constrain the model parameters. Subsequently, the dynamical landscape is explored by varying four parameters of interest: external current input to the neural populations, coupling strength between different brain regions, delay in the network, and noise level. The results show the presence of several dynamical regimes: at a coarse level, this can be divided into a state of no (or constant low) activity, an oscillatory state, and a state of high constant activity. The phase boundaries between those states are of special interest. Here we observe both multistability, as well as chaotic activity. These parameter configurations close to the bifurcation are strong candidates for task-dependent "operating points" that allow neuronal networks to perform information processing tasks. Interestingly, we also observe phase transitions within the oscillatory regime, between regions of full synchrony and chaotic behaviour, as well as an

intermediate one.
[1] Augustin, M., et al. (2017), *PLoS computational biology* 13(6).

Disclosures: C. Dimulescu: None. **N. Roth:** None. **K. Obermayer:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.16/DD5

Topic: I.06. Computation/ Modeling/ and Simulation

Support: DFG Collaboratory Research Center 910

Title: Applications of nonlinear control to the dynamics of the whole-brain network: A model study

Authors: *T. CHOUZOURIS, N. ROTH, K. OBERMAYER;
Tech. Univ. Berlin, Berlin, Germany

Abstract: Modulating and controlling neuronal activity is becoming increasingly important in clinical settings for the treatment of neurological disorders. In this study, we use a model-based approach to investigate the impact of external stimulation on the global dynamics of the brain. We implement a network model simulating spatiotemporal activity in the brain and, using methods from nonlinear control theory, we optimize the stimulation effects. The brain model's structural connectivity is constructed using Diffusion Tensor Imaging (DTI) data from the Human Connectome Project (HCP) divided into 90 cortical and subcortical regions according to the Automated Anatomical Labelling (AAL) atlas, each region corresponding to a node in the network. The node dynamics are defined by the phenomenological FitzHugh-Nagumo model, simulating the neuronal activity of each brain region. We systematically explore the network's state space for varying parameters, examine its dynamical landscape, and characterize the emerging dynamical network states. From there, we subsequently add external control to the nodes inducing transitions between these network states. Defining a minimization problem for the above system, we analyse the external stimuli that optimize the input energy and the deviation from the target state. We tune the number of controlled brain regions via applying sparse optimal control. This way, we transition from global to targeted, local stimulation. The sparse input signals allow us to examine the contributions of different brain regions to the network dynamics. We investigate the relation of these findings to the network topology and measures from linear control theory.

Disclosures: T. Chouzouris: None. **N. Roth:** None. **K. Obermayer:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.17/DD6

Topic: I.06. Computation/ Modeling/ and Simulation

Support: ERC Grant RG83283, 'FlexNeuro'

Title: Redundantly large networks can learn faster

Authors: *D. V. RAMAN, A. PEREZ ROTONDO, T. O'LEARY;
Dept. of Engin., Univ. of Cambridge, Cambridge, United Kingdom

Abstract: Large numbers of neurons often encode overlapping or identical task-relevant information. What is the reason for this apparent redundancy? We show how it allows for fast learning of generic tasks to high levels of performance, despite information-poor, noise-corrupted task feedback from teaching signals. More generally, we show how adding redundant neurons to an existing network architecture can increase robustness of the learning process to imperfect sensory information, synaptic noise, and task-irrelevant adaptive processes at the synapse. This allows redundantly large networks to achieve faster learning rates, and higher levels of performance post-learning. Our analysis does not rely on a particular choice of task or learning rule. Instead, we conceptualise learning a task as decreasing the value of an abstract task error function. This function can be visualised as a landscape, whose height represents the degree of error, and whose x-y co-ordinates represent the state of the adaptive network elements (e.g. synaptic weights). We show how adding redundancy 'flattens' the landscape in a mathematically quantifiable way, and how this allows for faster learning in the presence of task-independent plasticity processes (e.g. synaptic noise, the effect of learning other tasks, corrupted task-relevant sensory information).
Is every redundant neuron created equal? The degree to which an extra neuron improves learning performance depends on how it is incorporated architecturally into the network. We create an analysis template for comparing different ways of adding a neuron. We see that excessive redundancy can harm learning performance if synaptic strengths are intrinsically unreliable: the total degree of noisy synaptic plasticity then increases with network size. We also show that embedding a low-dimensional input signal into a very high dimensional space is a highly favourable form of redundancy. This corresponds to the cerebellar architecture, where low-dimensional input from mossy fibres undergoes a huge dimensionality expansion at the granule cell layer.
[1] Raman, Dhruva V., Perez-Rotondo, Adriana and Timothy O'Leary. "Fundamental bounds on learning performance in neural circuits." bioRxiv (2018): 508994. (accepted, PNAS)

Disclosures: D.V. Raman: None. **A. Perez Rotondo:** None. **T. O'Leary:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.18/DD7

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Learning complex action representations for goal-directed tasks through neuromodulation of Hebbian plasticity in modular spiking networks

Authors: *S. AENUGU, A. SHARMA, S. YELAMARTHY, H. HAZAN, P. S. THOMAS, R. KOZMA;
Univ. of Massachusetts Amherst, Amherst, MA

Abstract: Motivation: The computational models of decision making in basal ganglia primarily invoke actor-critic architectures from reinforcement learning (RL) theory. The phasic firing of dopaminergic neurons in response to an external reward is likened to the functioning of the critic which delivers the temporal difference prediction error as a teaching signal to the actor. In this study, we present an actor-critic framework which provides a theory about how complex action representations are learned with respect to specific goal-directed tasks in the presence of a neuromodulatory signal.
Methods: In this study we consider an agent navigating a maze with obstacles and stochastic state transitions. The state of the agent at any time is encoded using the place cell neurons and the actions are represented by neurons tuned towards specific directions. We incorporate a modular structure where a group of cells act as an intermediary between the place cells and action cells forming complex action representations. Structural credit assignment in such a network is accomplished by the neurons acting in a hedonistic fashion by locally optimizing their firing policy in response to the global modulatory signal broadcast by the critic. We implement a local policy gradient framework developed for interacting agents in RL theory[1] to update synaptic strengths between the neurons. We further prove theoretically that such a policy update is fundamentally equivalent to Hebbian synaptic plasticity. We use leaky-integrate-and-fire spiking neuronal model to simulate firing patterns of the neurons.
Results: The above modular spiking agent network learns to traverse the maze in fewer than 100 episodes. We average the learning curve over 100 trials to validate the robustness in learning. The variance in learning over multiple trials is further eliminated by incorporating neuronal ensembles and redundancy through population coding.
Conclusions: We formalized the concept of hedonistic neuron by defining a spiking neuron as an RL agent to account for neural coding of decision making and behavior. We thus provide a new convergent approach for training spiking neural networks using RL theory to solve goal-oriented tasks.

References:[1] Philip S Thomas. Policy gradient coagent networks. *In Advances in Neural Information Processing Systems*. 2011

Disclosures: S. Aenugu: None. **A. Sharma:** None. **S. Yelamarthy:** None. **H. Hazan:** None. **P.S. Thomas:** None. **R. Kozma:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.19/DD8

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Incorporating domain knowledge as a strategy for minimizing training requirements and improving generalization performance in convolutional networks applied to visual object recognition tasks

Authors: *A. S. RIOS[1], G. C. MEL[2], V. AKOPIAN[3], L. ITTI[1], B. W. MEL[1];
[1]USC, Los Angeles, CA; [2]Stanford Univ., Palo Alto, CA; [3]Google, Los Angeles, CA

Abstract: "Deep networks" (DNs) are inspired by the ventral visual processing stream, and can perform as well as humans on object recognition benchmarks. In other respects their behavior is very un-biological: (1) they require vast amounts of labeled data in order to learn, and (2) their generalization behavior is often very brittle. In particular, DNs can misclassify stimuli in ways that seem inexplicable to human subjects, and often perform poorly in learning tasks that require transfer or continual learning.
Our main hypothesis is that these undesirable performance characteristics result from the fact that layered DN architectures contain too many parameters, while lacking the proper representational biases needed to support rapid learning and natural patterns of generalization. Following the example of biological evolution, we hypothesized that generous incorporation of 3 types of domain knowledge can significantly reduce training requirements and improve generalization. These are: (1) laws governing natural image statistics; (2) the peculiar computing properties of neurons and neural circuits; and (3) the nature of the viewpoint-invariant object recognition task.
To begin to explore these hypotheses, we developed a new shape-intensive classification benchmark consisting of a 40K image subset drawn from the iLab 3-D object dataset (consisting of 10 classes of toy vehicles – cars, boats, planes, etc.; Borji et al, 2016]. To suppress all cues other than object shape, we randomized the hue and light-dark polarity of every input image on every presentation both during training and testing – producing unpredictably colorized images that nonetheless contained all of the original shape information. We compared classification performance using a fixed RESNET-18 network that received as input either (1) raw RGB (false color/polarity) pixel values vs. (2) explicit object boundaries detected by a sophisticated – but

fixed – commercial-grade contour-detecting front end (that also received false color/polarity RGB images as input). We found the compound network with shape pre-processing outperformed the conventional network (65.41% vs. 58.12% accuracy), suggesting that fewer modifiable parameters *would* have been needed by the compound network to achieve similar classification performance, a conjecture we are in the process of testing. Rigorous generalization tests of the two networks are also underway, as is development of a second stage of biologically-inspired shape pre-processing that we believe will further significantly reduce training requirements.

Disclosures: **A.S. Rios:** None. **G.C. Mel:** None. **V. Akopian:** None. **L. Itti:** None. **B.W. Mel:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.20/DD9

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Neural networks with motivation

Authors: *S. SHUVAEV[1], N. TRAN[1], M. STEPHENSON-JONES[1,2], B. LI[1], A. KOULAKOV[1];
[1]Cold Spring Harbor Lab., Cold Spring Harbor, NY; [2]Sainsbury Wellcome Ctr., Univ. Col. London, London, United Kingdom

Abstract: Motivational salience is a mechanism that determines an organism's current level of attraction or repulsion from a particular object, event, or outcome. In reinforcement learning, motivational salience is described by modulating the reward function by an externally controlled parameter that remains constant within a single behavioral episode. For example, the perceived reward associated with water is dependent on the current level of thirst; reward of food is determined by the level of hunger, etc. The vector of perceived values of various outcomes determines motivation of an organism toward different goals. Organism's behavior should be able to reflect the varying in time motivation vector. How can an organism adapt to behave effectively in conditions of different motivational contexts? Here, we propose a reinforcement learning framework that relies on neural networks to learn optimal behavior for different motivation vectors. First, we show that Q-learning neural networks, through function approximation, can learn to navigate towards variable goals whose relative salience is determined by a multidimensional motivational vector. Second, we show that a Q-learning network based agent with motivation can learn complex behaviors towards several goals distributed in an environment. Finally, we show that firing patterns displayed by neurons in ventral pallidum, a basal ganglia structure playing a crucial role in motivated behaviors, are

reminiscent of the responses of neurons in recurrent neural networks trained in similar conditions. In particular, similarly to pallidum neurons, artificial neural nets contain two different classes of neurons, tuned to reward and punishment. Overall, we suggest that motivation-based networks may generate complex ongoing behaviors that can adapt to dynamic changes in an organism's demands. Thus, neural networks with motivation can both encompass more complex behaviors than networks with a fixed reward function, and can be mapped onto neuronal circuits that control rewarded behaviors. Since animal performance depends on the states of satiety, wakefulness, thirst, etc., our approach should help build more realistic computational models that include these variables.

Disclosures: S. Shuvaev: None. **N. Tran:** None. **M. Stephenson-Jones:** None. **B. Li:** None. **A. Koulakov:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.21/DD10

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Relating information flow and causal interventions in neural circuits

Authors: *P. VENKATESH[1], P. GROVER[2];
[2]Electrical & Computer Engin., [1]Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Objective and Rationale
We propose a theoretical framework for understanding information flows, as well as the effects of interventions upon these flows, in neural circuits. We restrict our attention to event-related experimental paradigms, and seek an understanding of how information about the stimulus flows in these tasks. We extend our previous work *[Venkatesh et al., ISIT'19]*, which defined and identified information flow, by exploring the effect of causal interventions on these flows.
Methods and Results
Our theoretical framework is based on a graphical model of the brain: we treat the brain as being composed of different computational areas, or nodes, which interact with one another by transmitting random variables upon edges. Within this framework, we systematically define stimulus-related information flow with the help of information-theoretic measures. Our definition is one that is based on conditional mutual information, and provably satisfies intuitively desirable properties. Specifically, our definition guarantees the existence of "information paths" between input and output nodes of the graphical model, wherein all edges on the path carry information flow as per our definition *[Venkatesh et al., ISIT'19]*.
We then use techniques developed in the field of causal inference to understand the effects of causal interventions upon these information paths. Since our framework intrinsically accounts for

computational nodes which compute functions of their inputs, the model fits well within the framework of "Structural Causal Models". We show that if interventions on the stimulus produce causal effects at any node in the graph, then these nodes are guaranteed to have information flow to them, from the input nodes. We also present counterexamples to show that intervening on an information path *may not* cause effects on downstream nodes in the path. Likewise, the presence of causal effects due to interventions at a particular node does not imply an information path between these pairs of nodes.

Conclusions

Our work takes a systematic approach to defining information flow and explores the effects of causal interventions upon these flows. Such an approach has hitherto been lacking in other works that deal with information flow, including those based on Granger causality and Transfer Entropy.

Disclosures: P. Venkatesh: None. **P. Grover:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.22/DD11

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NIH Grant DC009659

Title: A new method for encoding sequence of sounds as words: A computational model of speech perception

Authors: *M. TOPALIDOU, G. HICKOK;
Univ. of California, Irvine, Irvine, CA

Abstract: In previous work, we proposed a novel method of encoding sequences by the synaptic weights of a speech production model that results in reduced spatial and temporal complexity compared to the existing proposed models. For example, speech production models generally contain buffers or working-memory modules to encode sequences (Bohland et al, 2010; Grossberg, 1978a) or use slots to label the kind of the unit (Foygel and Dell, 2000). The goal of this work is to demonstrate how the proposed sequence encoding in the weights emerges as a result of an initial learning of auditory-lexical association. Thus, we present a computational model of speech perception that learns the mapping between sound sequences and representations of individual words. The proposed model contains a lexical and auditory-phonological structures bidirectionally connected to each, which map onto the cortical regions of mid-posterior superior temporal sulcus/middle temporal gyrus (pSTS/pMTG) and posterior superior temporal gyrus (pSTG) respectively. Initially, the lexical units are randomly connected

in an all-to-all manner with the auditory-phonological units. Furthermore, a soft winner-take-all mechanism is implemented through self-excitatory and lateral-inhibitory connectivity among the units at each level. On each trial, input is sent to the 'phonemes' of a word with a short delay between them. The lateral inhibition among the auditory units results to a higher activity of the unit receiving a preceding input compared to its following one. The random connectivity between the two levels results in activation of only a few of the lexical units by these auditory units. At the end of each trial, Hebbian-learning is applied among the active units of the two levels. Analysis of the network behavior shows that after a simulation is completed, the lexical unit that represents a word is more strongly connected with the first 'phoneme' than the second one, and so on. This results from (i) the different maximum activity of the auditory-phonological units on each trial, and (ii) Hebbian-learning, where the more active a pre- and a post-synaptic unit are, the stronger they will be connected. A limitation of the model is that multiple lexical units can learn the same sequence, but also, in rare cases, a unique unit can learn multiple sequences. This might be remedied by adding a mechanism for pattern separation, e.g., modeling the function of the dentate gyrus in the hippocampus. To conclude, our model proposes a new method for encoding sequences in speech perception, that can easily be expanded to the encode of sequences in speech production as we previously introduced.

Disclosures: **M. Topalidou:** None. **G. Hickok:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.23/DD12

Topic: I.06. Computation/ Modeling/ and Simulation

Support: DBT–Wellcome India Alliance Intermediate fellowship IA/I/11/2500290
IISER Pune

Title: Balance of excitation and inhibition maximizes the coding capacity of a network

Authors: S. CHOWDHARY, *C. ASSISI;
Biol., Indian Inst. of Sci. Educ. and Res., Pune, India

Abstract: The sense of smell, movement patterning and selection, and episodic memories are all instantiated in the wetware of the brain as the spatiotemporal activity of networks of neurons. The capacity of a network to encode information may thus be thought of in terms of the number of stable spatiotemporal patterns it can generate. Purely excitatory networks often tend towards synchrony. Inhibitory networks, on the other hand, can generate elaborate and distinct patterns of activity. Earlier studies have mapped patterns of activity in an inhibitory network to a structural property of the network, namely its coloring[1]. Neurons associated with the same color do not

inhibit each other and fire in approximate synchrony, while those associated with different colors spike at different times. There are typically many ways to color a network. In fact, even determining all possible colorings of an arbitrary network is thought to be an intractable problem. This combinatorial explosion of possibilities also implies that a single inhibitory network can potentially generate a large number of spatiotemporal patterns. Here we ask, how many patterns can a network elicit (the capacity of the network), how stable are these patterns and can the network flexibly switch between different patterned outputs? To address these questions, we consider a small network (81 neurons) with a large number of possible colorings based on the popular puzzle, Sudoku. Each solution of the puzzle is a coloring of the network. We show that this, in turn, maps to a spatiotemporal pattern of activity generated by the network. There are nearly a trillion possible Sudoku puzzles (and a trillion possible spatiotemporal patterns). The stability of these patterns, thus the capacity of the network, is contingent upon the presence of excitatory interactions between the neurons. We show that a balance of excitation and inhibition maximizes the capacity of the network.
[1] A coloring of a network is a prescription that assigns different colors to nodes that are connected to each other.

Disclosures: S. Chowdhary: None. **C. Assisi:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.24/DD13

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Memory and cognitive capabilities of heterogeneous neural structures

Authors: *Y. G. T. TIRAT-GEFEN[1], A. TIRAT-GEFEN[2];
[1]Maxwave Res. LLC, Rockville, MD; [2]US Government, Rockville, MD

Abstract: This project evaluated whether heterogeneous cognitive processing elements (e.g. in a heterogeneous neural networks) representing artificial or biological cognitive systems can outperform structures of homogeneous processing elements (e.g. identical or nearly identical neurons in a neural structure).
Objectives of this research included: (i) to understand how to measure the similarity between the elements in the neural structure and to find the optimal dissimilarity level for maximum memory and/or cognitive processing capability; (ii) to evaluate the impact of random differences versus deterministic differences among neurons; (iii) the development of an analytical model for trade offs between similarity, memory capacity, and cognitive capabilities.
The methods used included a computational modeling to represent heterogeneous cognitive structures; an analytical mathematical model to measure the similarity between processing

elements or structures; and use of time-delays differential models to better represent biological neural structures. An emphasis was given to small grain neural structures, but other machine learning models were deployed to represent coarse grain heterogeneous structures in the brain, e.g. using reservoir computing or reinforcement learning models to represent large neural structures in the Basal Ganglia. Evaluated learning tasks included pattern recognition in images and time series.
The computational results indicated that slightly dissimilar structures have better memory and processing capabilities than homogeneous ones in many of the tasks evaluated; however these advantages are progressively lost as the degree of dissimilarity increases. This seems to mimic biological neural structures who exhibit a high level of similarity but are not solely composed of identical neurons. These findings are expected to help researchers to better understand how biological neural structures evolved; and to the development of new family machine learning methods using ensembles of heterogeneous processing elements.

Disclosures: Y.G.T. Tirat-Gefen: None. **A. Tirat-Gefen:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.25/DD14

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Effects of temporal clustering on learning in neural networks

Authors: *T. RAHIMI-MOGHADDAM, C. J. HONEY;
Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: MOTIVATION. Information arriving from the world is temporally clustered: two images seen consecutively (e.g. two items when shopping, or two plants when hiking) will tend to be more similar to one another than two images seen hours apart. How does the temporal clustering of information (i.e. training data) affect the speed and quality of what we learn? Temporal ordering is known to affect category learning in humans and in neural networks: learning prototypical items first is advantageous ("curriculum learning"), and "spaced" learning is often superior to "massed" learning. We aimed (i) to measure the effects of temporal clustering not only in supervised category learning, but also in unsupervised representation learning; and (ii) to identify biologically plausible learning architectures in which temporal clustering is especially advantageous for learning.
METHODS. Feedforward networks were trained to categorize visual stimuli (supervised learning) and autoencoders were trained to reconstruct the same stimuli (unsupervised learning). Training was performed using both backpropagation and target propagation. Temporal clustering of training data was parametrically controlled by drawing *n* consecutive samples from each

category.
RESULTS. Clustering of the training stimuli slowed learning in both category-learning and representation-learning. The effect was observed for all standard neural network architectures and learning rules. Drawing stimuli at random (the standard approach in machine learning) was superior to sampling with 2, 3, 4 or more consecutive exemplars from the same category. This effect was magnified when training employed mini-batches. A training protocol that eliminated all clustering was superior even to drawing stimuli at random (i.e. superior to the standard approach in machine learning research). These results generalized across MNIST and artificial datasets containing low category overlap.
CONCLUSIONS. We found any level of temporal clustering in training data, even the clustering that arises by chance in random sampling, slows down both category learning and representation learning in standard network architectures. This finding suggests that learning in artificial networks is optimal when the novelty of received information is maximized. However, a more biologically realistic neural architecture might still benefit from temporal properties of the information. Thus, our ongoing work examines biologically plausible learning architectures for which network dynamics capture the temporal structure of information, and where temporal clustering may itself be usable as a learning signal (Wiskott & Sejnowski, 2002).

Disclosures: T. Rahimi-Moghaddam: None. **C.J. Honey:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.26/DD15

Topic: I.06. Computation/ Modeling/ and Simulation

Support: LBNL-internal LDRD “Neural Systems and Engineering lab” (KEB)

Title: Optimal or random?: How correlated variability impacts population neural coding

Authors: *J. A. LIVEZEY[1,2], M. DOUGHERTY[1], S. MADHOW[1,2], P. SACHDEVA[1,2], K. E. BOUCHARD[1,2];
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Abstract: Neural computations take place in the presence of noise. Across repeated presentations of a fixed stimulus, neural measurements exhibit correlated variability (noise correlations). Measuring and understanding noise correlations are important for determining fundamental limits on the fidelity of neural representations. We address three outstanding issues in the field: what impact the choice of discriminability measure has on theoretical predictions, how to measure the optimality of observed noise correlations, and what correlational structures

in large networks should be experimentally observable.
Our first contribution is a prediction, based on theory, that noise correlations measured in areas of the brain that represent a set of stimuli as discrete or categorical, e.g., phonemes in STG (Chang, 2010), will have a different structure compared to those measured in areas of the brain that represent a set of stimuli as a continuous manifold, e.g., rotations of moving bars in retina (Franke, 2016, Zylberberg, 2016). Our second contribution is a new null model for testing whether observed noise correlations are optimal. Specifically, this null model tests whether there is optimal alignment between the principal axes of the observed noise correlations and the mean stimulus-responses for a given discriminability measure. By contrast, previously proposed null models only test whether measured correlations are more optimal than having no correlations but equal per-neuron statistics. When compared across diverse real and synthetic datasets, we observe a profound change in statistical significance, indicating that current null models cannot be used to test the optimality of observed correlations. Finally, we use simulations to determine what structured correlations in large networks of neurons (10^3 - 10^5) can be measured in experimentally realizable sub-populations (10 - 10^2). Together, these results provide an experimentally testable prediction for the structure of neural data and improved methods for testing hypotheses about the optimality of observed noise correlations.

Disclosures: **J.A. Livezey:** None. **M. Dougherty:** None. **S. Madhow:** None. **P. Sachdeva:** None. **K.E. Bouchard:** None.

Poster

523. Network Theory and Modeling

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 523.27/DD16

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Simons Collaboration on the Global Brain (SCGB) Grant AWD1004351
NSF CAREER Award IIS-1150186
NIMH grant (MH099611)

Title: Continuous-time partitioning of neural variability

Authors: *A. S. CHARLES, J. PILLOW;
Princeton Univ., Princeton, NJ

Abstract: Neural variability is ubiquitous in the brain and poses fundamental limits on the accuracy of neural codes. Recent work has shown that spike count variability in the early visual system can be partitioned into a modulatory gain component and a Poisson spiking noise component (Goris et al. 2014, Charles & Pillow 2017). However, these approaches examined spike counts in large (~1s) bins, and assumed the modulator to be: *(i)* constant for the entire

duration of each trial; and *(ii)* sampled independently across trials. This treatment ignores the fact that modulatory signals evolve continuously in time, and makes estimates of modulator variability highly dependent on the bin size used to count spikes.To overcome this shortcoming, we propose a model-based framework for continuous-time partitioning of neural variability. Our model describes both the stimulus-dependent firing rate and the time-varying modulatory signal with Gaussian Processes (GP). The observed spiking at every trial is then the sum of the stimulus GP and a noise GP passed through a nonlinearity. Our model significantly generalizes previous over-dispersion models by allowing estimation of a continuous-time spike rates. Specifically, the continuous-time noise GP allows our model to explain the difference in statistics across bin sizes by accounting for temporal correlations. Conditioned on estimates of the noise parameters, we can estimate the stimulus GP via a maximum *a-posteriori* optimization, using a Laplace approximation to marginalize over the noise process. While our model assumes a particular form for the non-stimulus contribution to spiking (i.e. the noise GP), there are many mechanisms that could cause such a contribution. Regardless, our model allows for the exploration of the effect of the relevant time-scales of these "noise" contributions, illuminating potential clues as to their sources and computational roles.

Disclosures: **A.S. Charles:** None. **J. Pillow:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.01/DD17

Topic: I.06. Computation/ Modeling/ and Simulation

Support: IITP grant funded by the Korea government (No. 2017-0-00451)

Title: Simultaneous EEG acquisition framework towards the massive EEG hyperscanning

Authors: ***S. LEE**[1], H. CHO[2], S. C. JUN[1];
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Abstract: Social interaction is one of the important activities of human beings and there are various efforts to understand the social interaction of people in recent years. As part of these efforts, investigators attempted to apply advanced acquisition system which simultaneously measures brain activities from massive subjects during social interaction, which is called hyperscanning. There has been recent work on how the brain responds to a competitive or collaborative paradigm in dyadic social interaction. In reality, interactions between the multilateral are very common as well as dyadic social interaction. In addition, beyond communication, there are also phenomena that only occur in a group such as Asch effect.

However, since research on current social interactions is quite limited in their methodology, most studies have focused on one-to-one situations. There are several reasons hardly to find hyperscanning studies among many persons. For example, a well-controlled experimental paradigm among multi-users is not easy to develop at a reasonably cheap expense. It is difficult to find a system that can measure a large number of people for research on group interaction. Therefore, in this study, we designed and developed a framework to acquire EEG signals at the same time in a large scale environment such as ten or more persons. The designed framework was modified repeatedly in a trial and error basis. Finally, our developed framework could simultaneously acquire the EEG signal from twenty persons wirelessly. In order to verify the developed framework, we performed watching emotion-evoking video experiments under the developed framework and successfully acquired brain signals from twelve users. It is believed that our developed framework may enable researchers to build their own signal acquisition systems for multi-users. It is expected that this system is able to utilize various studies such as crowd psychology, massive hyperscannning, many-to-many interaction, interactive contents development, and new BCI paradigm development. *Acknowledgments.* This work was supported by the Institute of Information & Communications Technology Planning & Evaluation (IITP) grant funded by the Korea government (No. 2017-0-00451)

Disclosures: S. Lee: None. **H. Cho:** None. **S.C. Jun:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.02/DD18

Topic: I.06. Computation/ Modeling/ and Simulation

Title: The influence of white matter lesions on the electrical field during transcranial electric stimulation. Preliminary results of a computational sensitivity analysis

Authors: *B. KALLOCH[1,2], K. WEISE[1,3], P.-L. BAZIN[1,4], L. LAMPE[1], A. VILLRINGER[1], M. HLAWITSCHKA[2], B. SEHM[1];
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Abstract: *Objective*: Individual simulation of transcranial electric stimulation (tES) holds the potential to predict the stimulation effect by providing insight into the subject-specific distribution of the electrical field. Transcranial direct-current stimulation is investigated as a means for facilitating recovery after a stroke. Numerical modeling on an inidividual basis becomes particularly important for this application due to the large variety in occurring stroke lesions. For this purpose, an accurate, individual head model is required. The influence of stroke

lesions on the electrical field was investigated before [Minjoli et al., 2017]. However, it is still unclear whether white matter lesions (WML), a phenomenon of the aging brain frequently found in stroke patients as well, must be considered for an accurate simulation. *Methods*: In this study, we are going to investigate the influence of WML on the distribution of the electrical field by a group-level sensitivity analysis of individual head models towards uncertainty in tissue conductivity based on [Saturnino et al., 2019]. We specifically focus on a high uncertainty in the conductivity of WML ([0.04,1.5] S m-1). Seventy-eight subjects, gender- (#: 39) and age-matched (yrs: 70.81 ± 3.39) are distributed across three groups according to their Fazekas score from 1 (F1) to 3 (F3) (mean, normalized, relative lesion volumes: F1=0.780 % ± 0.007 %, F2=2.550 % ± 0.024 %, F3=8.6800 % ± 0.0355 %). A dual electrode setup (10-20 coordinates: C3, C4) with 1 mA current strength is simulated. *Results*: We report the standard deviation of the computed the electrical field strength due to the uncertainty in tissue conductivity and analyze the individual contribution of the WML tissue uncertainty to the observed deviation. Preliminary results of one subject (F3) are reported from the mid-layer of the cortical gray matter. The electrical field strength (range: [0.015,0.258] V m-1) showed a 99th-percentile peak deviation of 0.038 V m-1 in the sulcal depths. The uncertainty in skull conductivity was the highest contribution to that deviation (47.55 %). The contribution of WML was 15.6 % and exceeded that of healthy white matter (5.47 %). *Conclusion*: Based on these preliminary results we expect a non-negligible contribution of WML to deviations in the electrical field strength, which we will confirm in our group study. Our results will inform whether changes of the aging brain must be considered for an accurate application of tES.

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Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.03/DD19

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Intel Labs

Title: BrainIAK education: User-friendly tutorials for advanced, computationally-intensive fMRI analysis

Authors: M. KUMAR[1], C. T. ELLIS[2], Q. LU[1], H. ZHANG[1], P. J. RAMADGE[1], N. B. TURK-BROWNE[2], ***K. A. NORMAN**[1];
[1]Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ; [2]Psychology, Yale Univ., New Haven, CT

Abstract: Advanced brain imaging analysis methods, including multivariate pattern analysis (MVPA), functional connectivity, and functional alignment, have become powerful tools in cognitive neuroscience over the past decade. These tools are implemented in custom code and separate packages, each requiring different software environments and language proficiencies to deploy for data analysis. Although usable by expert researchers, novice users face a steep learning curve. These difficulties stem from the need to learn a new programming language (e.g., Python), challenges in figuring out how to apply machine-learning methods to high-dimensional fMRI data, and missing or inadequate documentation and training materials. Furthermore, most standard fMRI analysis packages (e.g., AFNI, FSL, SPM) focus on preprocessing and univariate analyses, leaving a gap in how to integrate with advanced tools. To address these needs in the field, we developed BrainIAK (brainiak.org), an open-source Python software package that seamlessly integrates several cutting-edge, computationally efficient techniques with other Python packages (e.g., nilearn, scikit-learn) for file handling, visualization, and machine learning. As part of ongoing efforts to disseminate these powerful tools, we have developed user-friendly tutorials (in Jupyter notebook format) and exercises for learning BrainIAK and advanced fMRI analysis in Python more generally. These materials cover cutting-edge techniques including: MVPA (pattern classification and representational similarity analysis); parallelized searchlight analysis; background connectivity; full correlation matrix analysis; inter-subject correlation; inter-subject functional connectivity; shared response modeling; event segmentation using hidden Markov models; and real-time fMRI. For long-running jobs, with large memory consumption, we have provided detailed guidance on using high-performance computing clusters. These notebooks were successfully deployed and have been extensively tested at multiple sites, including as problem sets for advanced fMRI analysis courses at Yale and Princeton universities and at workshops and hackathons at Princeton, Yale, and Virginia Tech. We are excited to announce that these materials are now freely shared, with the hope that they become part of a growing pool of open-source software and educational materials for large-scale, reproducible fMRI analysis and accelerated discovery.

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Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.04/DD20

Topic: I.06. Computation/ Modeling/ and Simulation

Title: A mathematical framework to classify motivated mental states with EEG

Authors: *I. COS[1], N. IZAGUIRRE[3], M. GILSON[4], G. DECO[2];
[2]ETIC, [1]Univ. Pompeu Fabra, Barcelona, Spain; [3]Pompeu Fabra Univ., Barcelona, Spain; [4]Ctr. for Brain and Cognition, Barcelona, Spain

Abstract: How does social motivation influence motor behaviour? Although several studies have gradually dissected different aspects of motivation and have systematically probed specific brain areas responsible for them, we still lack a normative context capable of relating the expression of motivation on behaviour to its neural dynamics. Towards this end, here we investigate how social motivation influences movement parameters and decisions between actions, and investigate whether and how they reflect on changes of brain functional connectivity. Specifically, twelve human participants performed a decision-making paradigm, making choices between precision reaching movements. We manipulated the participants' motivated state by making the participant play either alone or with a simulated partner. In this context, the amount of reward obtained by the participant and by his/her partner was reported at the end of each trial, as a function of their end-point precision. No specific mention to competition was ever made to the participant. We simultaneously recorded kinematic, oculometric and EEG data. Our behavioural results show that end-point precision increased alongside with the partner's skill and that movement duration increased when playing with a partner, indicating a covert process of increased concern for performance whenever a partner was present. As a validation, we performed two complementary analysis of the subjects' electro-encephalographic recordings. First, a mental state discrimination analysis using several machine learning classifiers. Our results show that the mental states are best separable by means of the logistic classifier, with an 80-90% accuracy in most participants. Second, we performed an analysis of sources by means of a Functional Connectivity analysis, showing that the covert process of motivation includes significant changes on alpha-band sources in occipital areas. While these results require further testing, they clearly show that the presence of a partner modulates the participant's concern for performance, and that this responds to specific changes of functional connectivity typical consistent with the modulation of attentional load.

Disclosures: I. Cos: None. **N. Izaguirre:** None. **M. Gilson:** None. **G. Deco:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.05/DD21

Topic: I.06. Computation/ Modeling/ and Simulation

Title: NiBetaSeries: Assessing task connectivity

Authors: *J. KENT[1], M. VOSS[2];
[1]Neurosci., [2]Dept. of Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Resting state functional magnetic resonance imaging (fMRI) has enjoyed a privileged position as an assay of the functional connectivity of the brain. Task fMRI, on the other hand, has not been given the same privilege. The dominance of resting state fMRI is partially be driven by the ease of analysis relative to task fMRI. There are few tools that are designed to analyze the correlations of task evoked responses in task fMRI, and none that use the burgeoning Brain Imaging Data Structure (BIDS) for organization of inputs and outputs. NiBetaSeries fills this gap by utilizing minimally preprocessed data and raw data stored using BIDS to generate task evoked region to region correlations across the brain. NiBetaSeries is an open source BIDS application for the analysis of task evoked correlations, otherwise known as betaseries correlations. To test the validity and functionality of NiBetaSeries, we used freely available and simulated data.The open data we tested shows biologically plausible correlations between regions (Figure 1). We tested the validity of NiBetaSeries under different task conditions with simulated data. The simulated data show that higher signal to noise ratios have a dramatic impact on the ability of NiBetaSeries to accurately report region to region correlations. The overall results demonstrate NiBetaSeries as a working application for the analysis of task evoked correlations. NiBetaSeries helps to level the playing field between resting state and task fMRI by easing the process of analyzing task fMRI for connectivity.

Figure 1.
region-region beta series correlations from sub-01 from ds000164 (Verstynen, 2014) performing the Stroop task. The trial types within the stroop task could either be congruent, incongruent, or neutral. The subject's data was downsampled to 10x10x10 mm voxels in the tutorial to reduce compute time. The Schaefer (2018) atlas was used to combine voxels into meaningful regions.

Disclosures: **J. Kent:** None. **M. Voss:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.06/DP15/DD22

ControlExtraData.DynamicPosterDisplay:
Dynamic Poster
Topic: I.06. Computation/ Modeling/ and Simulation

Support: Swartz Foundation
NIH BRAIN Initiative grant R01 EB026949

Title: Non-parametric discovery of population dynamics from large-scale activity recordings

Authors: *M. GENKIN, T. ENGEL;
Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: Recent technological advances enabled activity recordings from hundreds of neurons simultaneously, opening an opportunity for neural population analyses. However, existing methods for extracting neural population dynamics from data lack either flexibility or interpretability. On one hand, methods fitting *ad hoc* parametric models to data are restricted to specific *a priori* hypotheses, which are not guaranteed to reflect the actual biological mechanism. On the other hand, the overparameterized models, such as artificial neural networks, are very flexible but difficult to interpret.

We develop an alternative non-parametric approach based on latent Langevin dynamics, which discovers an interpretable model of neural population dynamics from the data without *ad hoc* parametric assumptions. In our framework, changes of the neural population state over time are governed by a low-dimensional dynamical system, where driving forces can be continuously morphed to capture arbitrary non-linear dynamics. The activity of each neuron is related to the instantaneous population state via idiosyncratic firing-rate functions, which allow for heterogeneity of single-neuron responses. The driving forces and firing-rates are simultaneously optimized over the space of continuous functions to find a dynamical model that best describes the data. We develop a gradient-descent optimization algorithm that traverses the space of dynamical models of increasing complexity. To identify the model with the correct number of dynamical features, we develop a criterion based on a tradeoff between generalization accuracy and model complexity.

We show that our computational framework accurately recovers ground-truth population dynamics and firing-rate functions on synthetically generated datasets with biologically realistic amount of data. We demonstrate the scalability of our methods by recovering dynamics on large synthetic datasets (~150,000 spikes) of many neurons with diverse firing-rate functions. Our framework is suitable for analyzing multielectrode recordings with heterogeneous responses of

single neurons. It can be used to reveal mechanisms of neural computations on single trails and is broadly applicable to different behaviors and neural circuits in the brain.

Disclosures: **M. Genkin:** None. **T. Engel:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.07/DD23

Topic: I.06. Computation/ Modeling/ and Simulation

Support: NSF Grant DGE1745038
NSF Grant NCS-FO 183520
NIMH Grant 3R37MH066078-15S1

Title: Generating personalized brain models at high spatial resolution using Mesoscale Individualized NeuroDynamic (MINDy) Modeling

Authors: *M. SINGH, S. CHING, T. BRAVER;
Washington Univ. In St. Louis, St. Louis, MO

Abstract: Several recent initiatives have produced innovative whole-brain dynamical systems models of neural activity. Unfortunately, there remains a gap in systems neuroscience communities between generative models of brain dynamics vs. descriptive/statistical models of brain activity. Statistical models such as the functional connectivity matrix (FC) have proven highly amenable to data-driven characterizations of individual differences but do not allow for the overt construction of mechanistic hypotheses. In the current work, we aim to bridge this gap with a procedure to rapidly fit large-scale dynamical-systems models to individual subjects using fMRI. We propose a novel procedure to parameterize networks of hundreds to thousands of nonlinear neural masses (parcels) each with their connections, intrinsic decay, and a transfer function which converts activation to output. The procedure contains three main ingredients: 1) a new set of transfer functions to allow regional variation, 2) the use of a recent extension of stochastic-gradients for optimization, and 3) a new decomposition of connectivity into sparse and low-dimensional components. The last contribution proves key for high spatial resolution. Resting state HCP scans were preprocessed and deconvolved with a canonical hemodynamic response. Ground-truth tests indicate that the fitted parameters are valid and robust to both measurement noise and hemodynamic uncertainty. Parameters are highly reliable across sessions and robust to the choice of preprocessing method. The fits retrieve the true simulated individual differences in connectivity and discriminate whether/how individuals differ in connectivity or intrinsic dynamics. By contrast, we found that despite FC's strong discriminatory power (detecting if two subjects differ), individual differences in FC mapped poorly onto the underlying

differences in connectivity and systematic changes in FC can result from individual differences in purely local decay parameters. Lastly, we used the model weight matrices to make new inferences regarding directed connectivity. We observed that the strongest inhibitory sources were bilateral inferior frontal gyrus (IFG) pars opercularis which exhibited inhibitory directed connections to default mode regions. In contrast, the strongest excitatory source was left IFG pars triangularis with strong outward connections to the "language network". The current work therefore is an advance on two fronts: we have generated spatially-detailed biophysically plausible models which span individual human brains and, in the process, we have generated a new measure of connectivity.

Disclosures: M. Singh: None. **S. Ching:** None. **T. Braver:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.08/DD24

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Innosuisse (CTI) 25290.1 PFLS-LS
NIH Grant 1OT3OD025348-01

Title: Neurostimulation safety investigations performed with reference, posable anatomical models

Authors: A. M. CASSARA[1], ***B. A. LLOYD**[1], S. FARCITO[1], E. NEUFELD[1], N. KUSTER[1,2]; [1]IT'IS Fndn., Zurich, Switzerland; [2]ETH Zurich, Zurich, Switzerland

Abstract: Improved knowledge of the various parameters that influence unwanted peripheral nerve stimulation (PNS) during magnetic resonance imaging (MRI) is vital for the development of strategies to mitigate potential safety issues related to the latest generation of MRI scanners, which utilize higher gradients (e.g., for the Human Brain Connectome project [1]). Much better and more realistic virtual human models are needed to be able to achieve this goal. In this study, we evaluated the two recently developed anatomical phantoms for computational neurostimulation investigations, *Yoon-sun* (female) and *Jeduk* (male), created with high-resolution (0.1 – 0.2 mm) cryosection images from the Visible Korean Human project [2]. The phantoms feature more than 900 subject-specific nerve trajectories of separated sensory, motor (e.g., dorsal and ventral roots) and autonomic (e.g., vagus) nerves. The phantoms can also assume user-defined postures and can be morphed to permit model personalization, e.g., by changing the body-mass-index or by adapting morphology to target body shapes. Further, we extended our database of parameterized electrophysiological axonal models with recently developed separated models of myelinated sensory and motor fibers, and of an unmyelinated C-

fiber, to permit the development of customized neurostimulation models of nerves [3].
In a first step, PNS thresholds (slew rates and gradient field) and sites of stimulations were compared to experiments reported in the literature [4] to define experimental settings in terms of body positions and gradient pulse waveforms. This was complemented by investigating the effect of different electrophysiological models used to predict the threshold-pulse duration relationship described by Irnich [5] and Zhang [6]. We then identified via simulations three key combinations of body postures and positions that result in large variations in stimulation thresholds and sites of activations and used this information to perform validation experiments with volunteers in actual MRI environments.
Applications of our improved modelling pipeline include 1) scanning guidelines for, e.g., posture and position to reduce unwanted stimulation, 2) pulse sequence optimization – including stimulation reduction – as an additional goal or constraint, and 3) mechanistic inputs for low-frequency exposure guidelines.
[1] Nowogrodzki A. Nature. 2018; 563(7729)
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[6] Zhang B, et al. Mag Res Med. 2003; 50(1)

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Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.09/DD25

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Multiple electroencephalographic reading system with linear depth control in small species

Authors: *R. BELTRAN-RAMIREZ;
Sistemas de Informacion, Univ. De Guadalajara, Zapopan, Mexico

Abstract: The present invention describes an electrode movement system that allows to control the depth to which these (electrodes) are placed in the brain of the animal, for the performance of a continuous electrical activity monitoring (electroencephalographic record) in the animal to be evaluated.Said invention has a bluetooth module (connected to a microcontroller which are attached to the animal's torso allowing the mobility of this, while the microcontroller is connected to a series of motors and placed in a structure which is mounted on the skull of the

animal.
The system consists of a mounting structure composed of an octagonal piece which has an opening in the center that allows access to the brain of the animal, in addition to a series of holes in the surface for fixing this piece to the skull. On the surface of this piece there is an arrangement of pivots on which, for each pivot, a support for the electrode movement system is placed giving a total of 6 movement systems in total.The system test was performed under the following specifications.
Adult male rats of the Wistar strain of approximately 250 g of weight were used, which were kept under bioterium conditions: light / dark cycles 12 X12 h, temperature 22 ± 20 C and relative humidity of 50 ± 4% , with free access to water and food. For the implantation of the dialysis cannula and recording electrodes, the animals underwent stereotactic surgery under anesthesia with a mixture of halothane: carbogen (O2: 95: 5% CO2). A dialysis probe of 0.5 mm diameter and 2 mm in length, previously washed with HPLC quality water at a flow of 10 µl / min for 10 min and stabilized with a Krebs-Ringer solution at a flow of 2 µl / min, was inserted in the middle dorsal hippocampus (AP, -5.6mm; L, 4.2mm; V, 5mm from the pial surface). Two recording electrodes were placed bilaterally in the hippocampus; one of them attached to the dialysis cannula and the other in the contralateral region placed at the same depth. Two other electrodes were placed on the right and left entorhinal cortex (AP, -7.6mm, L, 5.2mm, V, 5mm) the EEG recording was started simultaneously in each of the electrodes for the study and analysis of the different areas as they are. Right Hippocampus, Left Hippocampus and cortex.
The use of the Multi-Electrode System helps several tests can be performed simultaneously which allow correlating each of the regions of which the EEG is performed.

Disclosures: R. Beltran-Ramirez: None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.10/DD26

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Evaluation of the Japanese eye typing system with EEG

Authors: *I. MOTOYAMA[1,2], T. UDA[2], M. YAMAZAKI[3], N. OKAMOTO[4], Y. KURODA[5], H. EDA[1,6];
[1]Grad. Sch. For GPI, Hamamatsu-Shi, Japan; [2]ORANGEARCH Inc., Tokyo, Japan; [3]GRAND COEUR LAB LLC, Saitama, Japan; [4]Col. of Social Sciences, Ritsumeikan Univ., Kyoto, Japan; [5]Kyoto Univ. of Educ., Kyoto, Japan; [6]Photonics Innovations Co., Ltd., Hamamatsu, Japan

Abstract: Introduction
Eye typing system has new possibilities of communication. It consists of an eye tracker, a virtual

keyboard, and software. The eye tracker needs a correct reference file for exact gaze point calculation. We have developed a Japanese eye typing system. We previously evaluated the novel eye typing system by the behavioral data (input time duration and its error) (Motoyama et al., SfN 2018). This time, we will evaluate the eye typing system through brain evaluation.

Method

The eye tracker (Tobii Eye Tracker 4C, Tobii AB, Sweden) was attached to the display, on which the virtual keyboard was shown. The 11x5 matrix was used as a Japanese "hiragana" virtual keyboard. We prepared a Fixed type virtual keyboard (FixVKB) and a Moving type virtual keyboard (MoveVKB), subject's reference files (subRef) and an others' reference file (othersRef).

The subject performed the eye typing of six words with each of the four conditions (Fix+sub, Fix+others, Move+sub, Move+others). We attached EEG electrodes (Fp1,Fp2,F7,F8,Fz,O1,O2 and Pz) according to 10-20 system and recorded the data using polymate II AP216 (MIYUKI giken Corp., Japan). Time-frequency analysis was applied to EEG data (Fz) to evaluate Fm theta activity and beta activities as an index of the concentration.

Eye movement were evaluated by Fp1, Fp2, F7 and F8 electrodes.

The consent form was obtained from all subjects. The experiment ethics and private information protection were fully considered.

Results

Fm theta was decreased association with the error inputs during the most complicated word (7 characters required 10 input, "me-i-ji-ji-n-gu-u"). Beta activities showed the increased tendency when the input duration was shorter compared with other input methods. Alpha activities were shown no tendency in any trials. During FixVKB, the number of eye movements was increased and the amplitude of the eye movements got enlarged compared to MoveVKB.

Discussion

Compared to the FixVKB, MoveVKB enables us to type more quickly and accurately without the stress. EEG also suggests the difficulty of the maintaining the concentration in FixVKB. Our study also shows that the difficulty of the eye typing can be objectively evaluated by combining the behavioral data and EEG data.

Disclosures: I. Motoyama: None. **T. Uda:** None. **M. Yamazaki:** None. **N. Okamoto:** None. **Y. Kuroda:** None. **H. Eda:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.11/DD27

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Brain Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry and ICT (2015M3C7A1029037)
Brain Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry and ICT (2017M3C7A1048092)
Korea Brain Research Institute funded by Ministry of Science and ICT (19-BR-02-07)

Title: Web-based integrated database platform for exploring and sharing omics datasets

Authors: J. CHOI, N. KIM, Y.-J. JANG, J. HEO, B. HA, *S.-J. JEONG;
KBRI, Daegu, Korea, Republic of

Abstract: It has been recently increasing to demand the data base platform for analysis of big data such as brain images and omics including proteomics and transcriptomics data in neuroscience field. Many database open to be shared, but most of them just provide the data obtained from experiments on their own interests and purposes, not such a kind of the platform. In this study, we created a web-based database system for searching, sharing, and analyzing the multiple data integrated by the open resources which are already existed. This system includes proteomics data, especially secretomes from extracellular vesicles (EV) of either neurons or astrocytes. REST(Representational State Transfer) service were adapted in our system to integrate the open resource such as datasets of Allen Brain Atlas and STRING DB. It allows users to get the information and compare them with their own data as well as the information of protein interaction. We usually used the SDK library to store the data in a web service, but the server was slow and stopped because of the high traffic and memory usage. Web-based RESTful service was utilized to develop lightweight, fast, scalable, and easy to maintain, so we used it. In order to visualize integrated data on the web, we have parsed the resource represented in XML as a DOM(Document Object Model) method and obtained the objects and visualized them as PHP language. Consequently, we established fundamental database platform with the omics data integrated by open resources. It is expected to be useful for researchers who want to compare and analyze their own data and several open data.

Disclosures: J. Choi: None. **N. Kim:** None. **Y. Jang:** None. **J. Heo:** None. **B. Ha:** None. **S. Jeong:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.12/DD28

Topic: I.06. Computation/ Modeling/ and Simulation

Title: Logistic regression applications for machine learning and intelligent decision-making

Authors: *H. C. YUAN[1], M. V. CHAO[2];
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Abstract: This poster investigates the application of logistic regression in machine learning and intelligent decision making. Examples of how logistic regression may be applied are also given from avionic systems. Logistic regression is a classification algorithm that is used to predict the probability of a categorical dependent variable using input that is continuous or discrete. Logistic regression is a statistical method for predicting binary classes. The outcome or target variable is dichotomous yielding only two possible classes. Logistic Regression is similar to linear regression, analyzing the relationship between a dependent variable and either one or multiple independent variables. Linear regression uses regular least-squares approach to compute the line of best fit to predict the value of the dependent variable based on the knowledge of the independent variable. Logistic regression produces an estimate of the probability of a certain event occurring. It uses the knowledge of an independent variable to predict if it is probable whether an event denoted by the dependent variable will either occur, or not occur, rather than to predict the actual value of this dependent variable. The dependent variable will be either 0 or 1, rather than being distributed along a line of best fit as in linear regression. Odds ratios are important to logistic regression as it is based on the probability of the occurrence of an event. The dependent variable in logistic regression is also known as a 'logit' (natural log of odds). Logistic regression as a classifier is more a linear classifier which uses the calculated logits (score) to predict the target class. Avionics in air traffic control in airports or in search and rescue often make intelligent decisions based upon airborne target kinematics (velocity, altitude) measured from sensor inputs. Logistic regression is a way to input airborne kinematic target data from sensors and make intelligent, categorical decisions for actions based on airborne target type. This poster examines the use of Logistic Regression binary classifier through an example of how intelligent decisions can be made through applying binary logistic regression with one-vs-rest multi-class classification schemes to airborne target velocity and altitude kinematic data for categorical decisions. As an application, this poster examines how binary Logistic Regression and multi-classification strategy can be applied to fuse avionics data (aircraft range, velocity) in decision making for classification, surveillance, and early warning decisions.

Disclosures: H.C. Yuan: None. **M.V. Chao:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.13/DD29

Topic: I.06. Computation/ Modeling/ and Simulation

Support: R01HL128546

R01HL139712
U54 HD090257

Title: Automatic segmentation of anatomical structures based on high-resolution diffusion tensor imaging in the developing pig brain

Authors: *J. LI[1], T.-W. TU[2], C.-H. HSU[2], A. AGARONYAN[1], V. LAM[1], K. LYDIC[1], A. DAVIS[1], P. C. WANG[2], A. V. FARIA[3], S. MORI[3], R. JONAS[4], N. ISHIBASHI[4];
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Abstract: BACKGROUNG Magnetic resonance imaging (MRI)-based atlases have become widely available for the human and mouse brain, allowing quantitative image analysis on a large scale in clinical and preclinical studies. Unlike rodents, the pig brain is gyrencephalic and has gray/white matter composition similar to the human brain, which offers various advantages as a translational animal model. Diffusion tensor imaging (DTI) is capable of characterizing detailed white matter structures and revealing subtle white matter abnormalities. However, a brain atlas for DTI has not been established in the piglet brain. OBJECTIVE Our project aims to develop a DTI-based 3D piglet brain atlas that includes detailed white matter regions. Aim of the present study is to evaluate the feasibility of automatic parcellation of brain regions to perform regional quantitative image analysis using the unique piglet model. METHODS We used 7T MRI to acquire a high resolution ex-vivo DTI brain image of a 6-week-old female Yorkshire pig. All identified regions were traced and labeled manually using ROIEditor (Johns Hopkins University) based on a DTI directionally-encoded color map and anatomical information from previous atlases (Saikali, 2010). The acquired ROIs templates were applied on the brain images normalized by Diffeo Map (Johns Hopkins University) for automated parcellation. RESULTS We isolated 131 individual cerebral structures including 16 paired cortical and peripheral white matter areas, respectovely. Deep brain white matter regions such as coronal radiata, internal capsule, superior longitudinal fasciculus, and sagittal stratum were successfully differentiated. The quality of automatic delineation was validated by measurements of (1) dice index, (2) mean standard deviation, and (3) fractional anisotropy intensity of each region. The results showed a high correlation between the manual ROI-based and the automated approaches in most regions. CONCLUSION Our piglet brain atlas can facilitate group analysis of DTI data in a majority of brain regions. Introducing advanced meuroimaging technologies and an atlas-based approach to the piglet model will provide a wealth of bidirectional information to assist research directed toward complex human brain development and a wide range of neurodevelopmental disorders.

Disclosures: **J. Li:** None. **T. Tu:** None. **C. Hsu:** None. **A. Agaronyan:** None. **V. Lam:** None. **K. Lydic:** None. **A. Davis:** None. **P.C. Wang:** None. **A.V. Faria:** None. **S. Mori:** None. **R. Jonas:** None. **N. Ishibashi:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.14/DD30

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Texas Institute of Brain Injury and Repair(TIBIR)

Title: Computational methods for registration and analysis of whole brain volumetric image data acquired via serial two-photon tomography

Authors: *A. D. AJAY[1,2], D. M.RAMIREZ[1,2], K. POINSATTE[1,2], M. P. GOLDBERG[1,2], J. P. MEEKS[1,2,3];
[1]Dept. of Neurol. and Neurotherapeutics, UTSouthwestern Med. Ctr., Dallas, TX; [2]Peter O'Donnell, Jr. Brain Inst., [3]Dept. of Neurosci., Univ. of Texas Southwestern Med. Ctr., Dallas, TX

Abstract: The UT Southwestern Whole Brain Microscopy Facility (WBMF) provides access to a variety of automated microscopy platforms which enable acquisition of high resolution, volumetric images of the mouse brain. Such images can be used to interrogate the brain-wide distribution of labeled features of interest, including neuronal circuit connections which may be altered in models of brain injury or disease. We have developed a flexible and robust computational pipeline to effectively visualize and quantitate whole brain serial two-photon tomography (STPT) datasets acquired on the TissueCyte 1000 platform. The two main functions of the pipeline consist of signal segmentation and image registration. Various fluorescent signals of interest (*e.g.* neuronal somas or processes, vascular signals, etc.) are first segregated using an open-source machine learning based software toolkit (Ilastik; www.ilastik.org) to perform pixel classification using a supervised random forest classifier, which is then applied uniformly to large cohorts of whole brain datasets. Prediction probability maps indicating how accurately a pixel is classified into one of the user-defined classes are then exported. The segmented signals are displayed visually as a TIF stack for detailed 3D rendering and each experimental brain dataset can then be spatially aligned to the reference atlas (Allen Institute for Brain Science Common Coordinate Framework v3.0 (CCF v3.0)) for quantification. Applying the registration transform to the Ilastik-generated prediction probability maps and segmentation enables quantification of the voxel density in each segmented brain region. Our pipeline incorporates the SimpleElastix registration library, a collection of high performance medical image registration algorithms, which has allowed us to carefully choose transformation models and tune their parameter maps to achieve very good global and local registration results. Additionally, we have used an extension of the Insight Registration and Segmentation toolkit allowing registration of full resolution images. Validation measurements for Ilastik classification, image registration, and

measurements of regional volume changes are in process. The image analysis pipeline has been used to study circuit plasticity following ischemic stroke and we anticipate it will be useful for a wide variety of experimental paradigms including different injury and disease models as well as labeling strategies.

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Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.15/DD31

Topic: I.06. Computation/ Modeling/ and Simulation

Support: CONP Research Scholar Award

Title: Automated alignment and segmentation of mouse mesoscale brain images using machine learning

Authors: *D. XIAO, B. FORYS, R. TANDUN, T. MURPHY;
Dept. of Psychiatry, Kinsmen Lab. of Neurolog. Res., Univ. of British Columbia, Vancouver, BC, Canada

Abstract: Quantitative analysis of large scale brain images relies on accurate alignment and segmentation of regions of interest. Matching a reference atlas to the brain data are very labor- and time-intensive manual tasks and prevent high-throughput analysis. Furthermore, human error may occur when clicking the anatomical landmarks in different subjects. Machine learning-based alignment and segmentation approaches for brain images are gaining interest due to their self-learning and generalization ability when applied to large amounts of data. As machine learning architectures are becoming more mature, they gradually outperform previous state-of-the-art classical algorithms. Our aim is to develop an automated machine learning-based alignment and segmentation approaches for quantitative mouse mesoscale brain images. We first trained a deep learning model to identify specific landmarks (i.e. bregma, lamda) in a wide-field calcium imaging dataset from more than 200 transgenic mice. The model can then automatically label landmarks in a new dataset of calcium images with high accuracy. Furthermore, automated brain atlas segmentation onto the calcium images was then performed using a fully convolutional network based on previously labelled landmarks and sensory mapping (via visual/whisker/vibration stimulation). The model can be further optimised by training on a larger datasets and capable of processing large-scale brain images automatically under a few minutes. We propose to further demonstrate that our method significantly enhances the accuracy and robustness of alignment and segmentation of new data sets.

Disclosures: **D. Xiao:** None. **B. Forys:** None. **R. Tandun:** None. **T. Murphy:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 524.16/DD32

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Simons Foundation SCGB 543015

Title: Inference of decision-making strategy from high throughput animal training

Authors: ***M. QIAO**, T. ZHANG, C. SEGALIN, S. SAM, P. PERONA, M. MEISTER; Caltech, Pasadena, CA

Abstract: Understanding cognitive functions usually requires training animals to perform complicated decision-making tasks. During the course of training, the animal changes its strategy for decision-making. It is important to figure out the strategy each animal uses at any given trial in order to understand animal learning. Understanding how individual animals learn will require high-throughput standardized methods for behavioral training but also advances in the analysis of the behavioral data. In the course of training, an animal may change its behavior abruptly, and capturing such events calls for a trial-by-trial analysis of the animal's strategy. To address this challenge, we developed an integrated platform for automated animal training and analysis of behavioral data. A low-cost and space-efficient apparatus serves to train entire cohorts of mice on a decision-making task under identical conditions. A generalized linear model (GLM) analyzes each animal's performance at single-trial resolution. This model infers the momentary decision-making strategy and can predict the animal's choice on each trial with an accuracy of ~80%. We also assessed the animal's detailed trajectories and body poses within the apparatus. Unsupervised analysis of these features revealed unusual trajectories that represent hesitation in the response, reflect a behavioral adjustment to prevent further mistakes. We are now extending the study to behavioral paradigms in which the optimal decision-making strategies change from block to block, and preliminary results suggest that the model faithfully captures each animal's strategy in each block. These efforts promise to accelerate the understanding of animal learning and decision-making.

Disclosures: **M. Qiao:** None. **T. Zhang:** None. **C. Segalin:** None. **S. Sam:** None. **P. Perona:** None. **M. Meister:** None.

Poster

524. Computational Tools for Brain and Behavioral Experiments

Location: Hall A

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Program #/Poster #: 524.17/DD33

Topic: I.06. Computation/ Modeling/ and Simulation

Support: Consolidator Grant, LS5, ERC-2016-COG

Title: Machine learning techniques for online decoding of single units activity and position during wakefulness or sleep reactivation

Authors: *T. BALENBOIS, S. LAVENTURE, D. BRYZGALOV, K. BENCHENANE;
Mobs Team, Lab. Plasticité Du Cerveau, ESPC, Paris, France

Abstract: The hippocampus is crucial for spatial navigation and place cells are considered to be the underlying neural substrate. Seminal studies have already shown that position can be decoded from place cell activity. Accessing this neural spatial information in real time would enable researchers to induce learning based directly on neural activity patterns by pairing the decoded position with rewarding or aversive stimulation. However this requires faster decoding methods than are currently available. A significant effort in the field right now is directed towards sorting spikes in real time in order to access the activity of single units which can then be used to decode position. Examples of this include using template matching or expectation maximization. Alternative methods consist of avoiding the spike sorting step and using a bayesian model to decode position based on unsorted spikes. Nevertheless, most of these tools present the usual trade-off between accuracy and efficiency. Using machine learning tools that can sustain both accuracy and computational efficiency is a mandatory condition for aversive or appetitive learning experiments based on decoded position. We used artificial neural networks to decode single unit activity ; this initial step is then followed by a classical approach consisting of a combination with a simple bayesian model to then decode the position of an animal given its place cell activity. We show that the accuracy is similar to that of offline decoding. The accuracy is a function of the number of active place cells recorded. Additionally, the integration of single unit activity has to be done on a biologically relevant time window. Our decoding device works with a time precision of 15 to 30 ms, which is consistent spatial coding in the hippocampus. Altogether, this shows the feasibility to use artificial neural networks as machine learning tools to decode position in real time.

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Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.01/DD34

Topic: I.07. Data Analysis and Statistics

Support: NARSAD Young Investigator Grant (Sanders)

Title: Automated atlas refinement in 3D

Authors: *D. M. YOUNG[1], S. FAZEL DARBANDI[1], G. SCHWARTZ[1], Z. BONZELL[1], D. YURUK[1], M. NOJIMA[1], J. RUBENSTEIN[1], W. YU[2], S. SANDERS[1];
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Abstract: We present Magellan, a suite of software tools to transform 2D organ atlases into consistent 3D atlases, and demonstrate the benefits by comparing the performance in cleared mouse brain samples at single nuclei resolution. Atlases are critical for mapping sample data into the correct anatomical space for quantification and comparison across multiple samples. Atlases across species and organs have been generated typically by serial labeling of 2D planes, a time-consuming task that can lead to inconsistencies and artifacts such as boundary misalignments between planes apparent in orthogonal dimensions. The expanding field of whole-organ volumetric microscopy necessitates complete, accurate, and fully 3D atlases, and variability across development mandates the generation of such atlases at specific developmental stages. To generate such atlases, while leveraging and cross-referencing existing atlases, we developed automated methods to extend atlases from serial 2D to fully 3D whole-organ maps. We employ 3D smoothing techniques to minimize region boundary artifacts in all dimensions while maintaining each region's overall shape and placement. To further refine labels, we automatically identify and incorporate gross anatomical boundaries into existing atlases to improve correspondence between labels and underlying anatomical markers, including those that may not have been as apparent along a single axis. Using the Allen Developing Mouse Brain Atlas series, we apply these methods to each atlas from prenatal to adult stages to demonstrate improved label coverage and anatomical correspondence across development as measured by distances between gross anatomical and label borders and within-region variability in 3D. Applying the atlas refinements to quantification of C57BL/6J mouse brains at age P0, we replicate these enhancements on intact tissue cleared brains including whole-brain nuclei detections with a 37% improvement in anatomical boundary match ($p_{adj} = 0.007$; n = 15 mice, 10 male and 5 female) to demonstrate closer atlas alignment and improved regional quantification at both the gross anatomical and cellular levels. Magellan-transformed atlases improve the analysis of whole-

organ volumetric microscopy data facilitating the direct comparison of 2D and 3D data registered to the Allen Brain Atlas and equivalent resources.

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Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.02/DD35

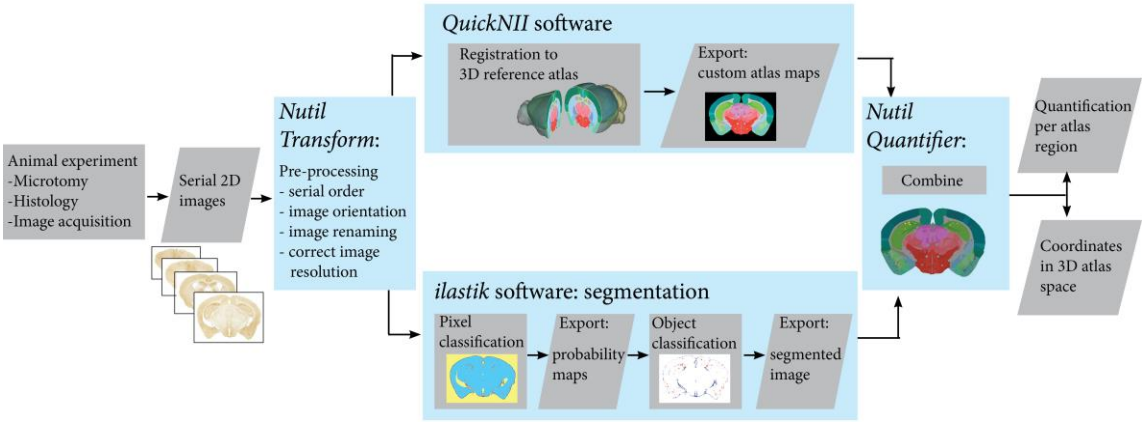
Topic: I.07. Data Analysis and Statistics

Support: European Union's Horizon 2020 Research and Innovation Programme under Grant Agreement No. 720270 (HBP SGA1) and 785907
EU JPND project CrossSeeds, NFR Grant 247995

Title: Workflow for quantification and spatial analysis of labeling in large series of microscopic images from murine brains

Authors: *M. A. PUCHADES, S. C. YATES, N. GROENEBOOM, G. CSUCS, T. B. LEERGAARD, J. G. BJAALIE;
Inst. of Basic Med. Sci., Univ. of Oslo, Oslo, Norway

Abstract: Introduction: Experimental research in small animal disease models often require quantitative comparisons of cellular and molecular measures in large groups of specimens, with need for efficient and reproducible methods. We present a novel workflow for quantification and spatial analysis of labeling in large series of section images from mouse and rat brains, using Human Brain Project (HBP) tools and procedures. Method: As a first step, whole brain image series are anchored to a digital reference brain atlas, using the software tool *QuickNII*, to produce accurate anatomical maps adapted to the orientation of the images. Subsequently, we use advanced automated image segmentation using machine learning with *ilastik* based on Random Forest Algorithm for supervised classification. The classified images are subsequently analyzed on a whole brain and regional level with input from the atlas maps with the *Nutil* software. Results: The number of objects (extracted features) and areas occupied by the objects are identified at the whole brain and region level, enabling quantitative analysis. This workflow yields results comparable to expert manual delineations and to the output of a stereological method.



Disclosures: **M.A. Puchades:** None. **S.C. Yates:** None. **N. Groeneboom:** None. **G. Csucs:** None. **T.B. Leergaard:** None. **J.G. Bjaalie:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.03/DD36

Topic: I.07. Data Analysis and Statistics

Title: Automatic ultrasound based neuronavigation approach for functional ultrasound imaging

Authors: M. NOUHOUM[1,2], J. FERRIER[2], B. OSMANSKI[2], M. TANTER[1], *T. DEFFIEUX[1]; [1]Physics For Med. Paris (Inserm / ESPCI Paris / CNRS / PSL Res.), Paris, France; [2]Iconeus, Paris, France

Abstract: Functional ultrasound (fUS) is a recent imaging technique capable of mapping cerebral vascular network but also to capture neuronal activity with very high sensitivity. One remaining hurdle is the expertise required to position the probe and identify brain structures solely based on 2D vascular images, especially when it comes to oblique non-coronal and non-sagittal slice. In this study, we developed and validated a fully automatic and integrated approach combining 3D multi-slice ultrasensitive Doppler imaging of the mouse brain and online automatic registration to the reference 3D anatomical atlas from the Allen brain institute. Using a prototype fUS scanner (Iconeus, Paris, France) equipped with a 15MHz ultrasonic probe (128 elements, 0.1-mm pitch) mounted on a motorized setup, successive 2D transcranial images were acquired in a male C57BL/6 mouse anesthetized with 1.5% isoflurane. Linear scans were repeated in several directions using a tomographic approach and reconstructed to obtain a high-resolution (100 x 100 x 100 µm3) 3D isotropic volume of the mouse brain vasculature. This 3D volume was first registered on a set of Magnetic Resonance Angiography scan acquired on a C57BL/6 mice along with T2-weighted images for anatomical correspondence and co-registered

scans were then aligned to the Allen Mouse Brain atlas.
The 3D Doppler volume was then used as a reference for automatic non-rigid datasets registration within experiments using an iterative optimization algorithm based on intensity matching of big vessels.
Validation was performed on C57BL/6 mice anesthetized with a Ketamine/Xylazine mixture. A caudal-to-rostral linear fUS scan has been acquired through the skin and skull (0.2 mm step, 8mm length, 60 s duration).
The prototype software was used to automatically register the scans onto the reference and thus on the atlas. An oblique 2D imaging plane was chosen to encompass both the left S1BF and right V1 cortex regions and the probe was moved automatically after selection. Functional imaging following whisker and visual stimulations revealed strong activation of both cortical seeds, validating the plane positioning. Secondly, automatic resting-state connectivity matrix could be constructed with 44 regions and demonstrating strong bilateral connectivity within the cortex as expected.
The proposed functional ultrasound online neuronavigation approach enables non-expert automatic brain navigation and positioning for standardized experiments and protocols and could also pave the way to software guided injection in deep structures.

Disclosures: **M. Nouhoum:** A. Employment/Salary (full or part-time):; Iconeus. **J. Ferrier:** A. Employment/Salary (full or part-time):; Iconeus. **B. Osmanski:** A. Employment/Salary (full or part-time):; Iconeus. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. **T. Deffieux:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. F. Consulting Fees (e.g., advisory boards); Iconeus.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.04/DD37

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant K01HD091283
NIH Grant P2CHD06570

Title: Braindrles: A crowd-sourcing tool for stroke lesion segmentation quality control

Authors: ***S.-L. LIEW**[1], A. SURI[1], M. P. NOTTER[2], K. ITO[1], P. RAAMANA[3], A. KESHAVAN[4];
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Abstract: Understanding how a stroke affects the brain requires quantification of how the stroke infarct interferes with existing brain structures. For instance, stroke lesion overlap with the corticospinal tract is a robust predictor of sensorimotor recovery, while lesion overlap with Broca's area is a key predictor of recovery in the language domain. Although manual segmentation is the gold standard for lesion segmentation, this approach is extremely time consuming and requires expertise in neuroanatomy. Emerging big data approaches for stroke rehabilitation research requires automated approaches for analyzing hundreds to thousands of stroke MRIs (e.g., ENIGMA Stroke Recovery). A fast, accurate, and scalable pipeline for lesion segmentation is thus desperately needed. We generated a publicly-available dataset of 304 manually segmented lesion masks and used this to determine the best existing automated lesion segmentation algorithm (LINDA, Lesion Identification with Neighborhood Data Analysis). However, although LINDA performs well, there is still a significant need for manual visual inspection to ensure the automated lesion masks are correct, which creates a bottleneck. To this end, we developed a novel, crowd-sourced platform for gamified visual quality control of lesion masks called Braindrles (https://braindrles.us). Braindrles utilizes the same web-based platform as its predecessor Braindr, which harnessed the power of citizen scientists to provide over 80,000 human annotations on structural MRI motion artifacts. Braindrles provides a mobile optimized annotation interface in which citizen scientists are shown dynamic triplanar images of stroke MRIs with lesion segmentation overlays, which are animated to facilitate quick judgements of segmentation accuracy. Citizen scientists are asked to swipe right if the lesion segmentation accurately captures the lesioned territory and left if the segmentation is incorrect. Citizen scientists are onboarded with a tutorial, and images with ground truth segmentations are randomly included in the database to evaluate each individual's accuracy. Votes, weighted by individual accuracy, are aggregated and used to determine acceptable lesion segmentations versus those that need to be manually corrected. This information is used to inform and improve machine learning lesion segmentation algorithms. Overall, Braindrles employs a unique citizen-science approach to expediting visual quality control and has the potential to rapidly advance large-scale stroke rehabilitation research and lesion segmentation algorithm development.

Disclosures: S. Liew: None. **A. Suri:** None. **M.P. Notter:** None. **K. Ito:** None. **P. Raamana:** None. **A. Keshavan:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.05/DD38

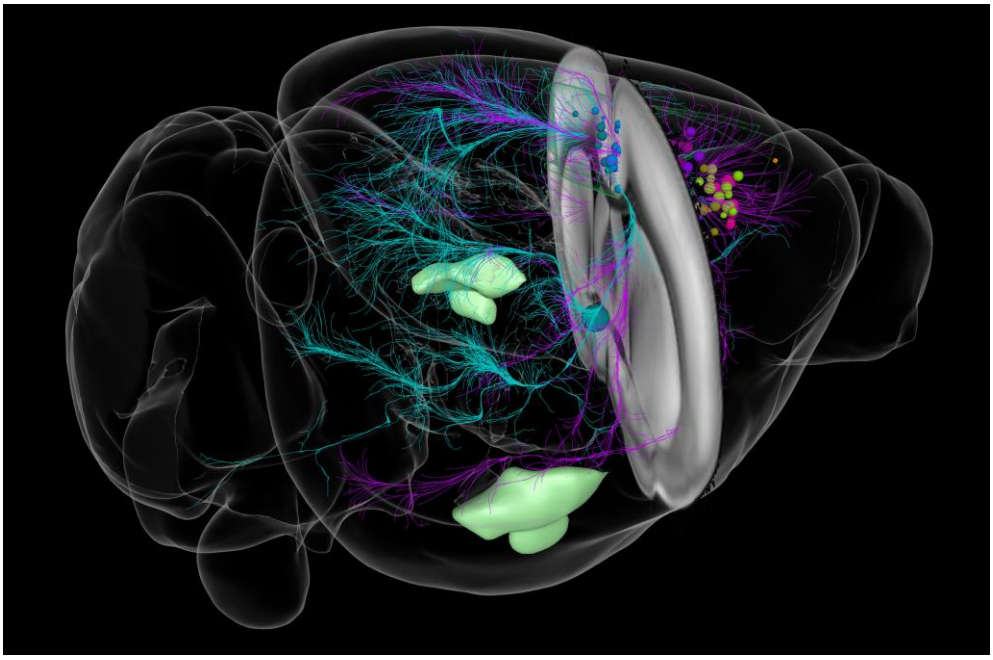
Topic: I.07. Data Analysis and Statistics

Support: FLAG ERA project FIIND (NWO 054-15-104)
European Union's Horizon 2020 Framework Programme for Research and Innovation under Grant Agreement No 785907 (Human Brain Project SGA2)

Title: SBA composer: Web-based platform for interactive, multi-modal data visualization with Jupyter notebook control

Authors: R. BAKKER, N. TIMONIDIS, ***P. H. TIESINGA**;
Donders Ctr. for Neurosci., Radboud Univ., Nijmegen, Netherlands

Abstract: We present SBA Composer, an interactive online platform for visualizing brain volumes, tissue sections, region meshes, neuron morphologies and other 3d geometries inside a brain atlas. The platform uses brain atlases from the set collected by the Scalable Brain Atlas [Bakker et al (2015) Neuroinformatics, 13, 353-366]. They minimally consist of a brain region hierarchy, meshes for each brain area, one or more reference data volumes and a definition of the template space. Data can be imported into Composer either interactively by the user or programmatically from within a Jupyter notebook or via 3rd party websites, which can open SBA Composer as a separate tab in the browser and send data/receive messages from it.
A key challenge of multi-modal integration is the alignment of the various data sources. If they are pre-aligned to the selected atlas, they may still differ in the choice of units, orientation and origin. Composer offers a data import wizard to correct these settings, and uses the brain addressing system (brainaddress.org) to refer to location in the brain. For unregistered data, interactive tools for scaling, translation and rotation are available, as well as point-pair based registration.
A first use case is the Connectomic Composition Predictor (CCP), a service developed for the Human Brain Project (HBP) which predicts a mouse connectivity matrix on the basis of gene expression data. The service runs in the HBP Collaboratory, which provides Jupyter notebook environment in which python scripts can be run interactively. The CCP visualization module opens an SBA Composer window and loads the predicted connectivity as a volume, which is displayed as one or more section planes at arbitrary angles.
A second use case is the inspection of connectivity experiments from the Allen Institute. These experiments result in projection densities, which can be displayed as 'streamlines' and represent efferent connectivity from the injected area. In the figure, we inspect whether injections in the Anterior Cingulate Area are connected to the Basolateral Amygdalar nucleus.



Disclosures: **R. Bakker:** None. **N. Timonidis:** None. **P.H. Tiesinga:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.06/DD39

Topic: I.07. Data Analysis and Statistics

Title: Deep learning for OCT angiogram vectorization

Authors: ***S. STEFAN**, C. POLUCHA, J. LEE;
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Abstract: Optical coherence tomography (OCT) is a rapid, label-free, high resolution imaging tool that is becoming increasingly popular and useful for neuroscientific study. OCT may be particularly useful for the analysis of vascular networks, which are visualized based on dynamic scattering in vessels due to moving blood cells. One promising application of OCT is in the lifespan tracking of microvascular alterations in neurological diseases such as Alzheimer's Disease, without the need for contrast agents, additionally allowing measurements of blood flow in penetrating arterioles and venules using Doppler OCT as well as blood flow velocity in capillaries. However it is not realistic to semi-manually segment and vectorize a large number of longitudinal OCT datasets using existing methods. Additionally, many methods applied to the segmentation of the vasculature using other imaging modalities (for example two-photon

microscopy) are not as successful on OCT angiograms due to the effects of multiple-scattering which results in projection artifacts or “tails”. To combat this issue, we have trained a deep convolutional neural network to automatically segment OCT angiograms, using labeled data consisting of angiograms that are fully segmented and manually corrected. Application of our network to unseen test data of standard angiograms yields promising results, performing significantly better than standard methods of vessel segmentation without the need for empirical parameter optimization. Segmented data can now be vectorized more easily and accurately, making it possible to quantitatively investigate questions concerned with angioarchitecture, blood flow and neurovascular coupling.

Disclosures: **S. Stefan:** None. **J. Lee:** None. **C. Polucha:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.07/DD40

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R24 MH114805
NIH Grant F99 NS108557

Title: Introducing bioimage suite web: A simple, modern, & powerful software suite

Authors: ***S. NOBLE**, Z. SALTZMAN, C. LACADIE, H. GARBUS, J. ONOFREY, X. PAPADEMETRIS, D. SCHEINOST;
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Abstract: Neuroimaging research to dissect the functional organization of the brain is a rich and rapidly growing area of study, buoyed by support from major public initiatives. However, neuroimaging software infrastructure has lagged behind; notably, the most powerful software often require computational expertise beyond the scope of most neuroscience labs. Here, we introduce a state-of-the-art neuroimaging architecture that overcomes these limitations through an easy-to-use yet powerful design. BioImage Suite Web (BISWeb; www.bioimagesuite.org) is a point-and-click app that runs in any modern web browser without any installation necessary, yet with performance rivaling that of a locally installed software. Due to the general nature of its architecture (JavaScript, C++, WebAssembly), BISWeb works on most modern web-browsers (e.g., Chrome, Safari, Firefox), major operating systems (e.g., macOS, Windows, Linux), and devices (e.g., tablets, smartphones). BISWeb currently supports a range of functionality in human and animal fMRI: defacing, segmentation, registration, and more. New additions include visualizations that summarize the connectome, automatic brain segmentation via deep learning, and a DICOM to BIDS format converter. Furthermore, all BISWeb applications read and write

all data and parameters used in analyses to a JSON file, alongside software version, operating system, date, and user data. This enables a workflow in which a user can load data, create visualizations, and save their state to continue work later. These files can also be used to share "live figures" with collaborators or validate analyses and software across updates. A wealth of guidance is already available for new users, from YouTube video tutorials to developer documentation (all code is openly available on GitHub). In summary, BISWeb is a modern web-based neuroimaging software created not only to make state-of-the-art analysis accessible to users of any skill level, but also to ensure results are both transparent and reproducible. These goals promote rigor in the bourgeoning field of neuroimaging.

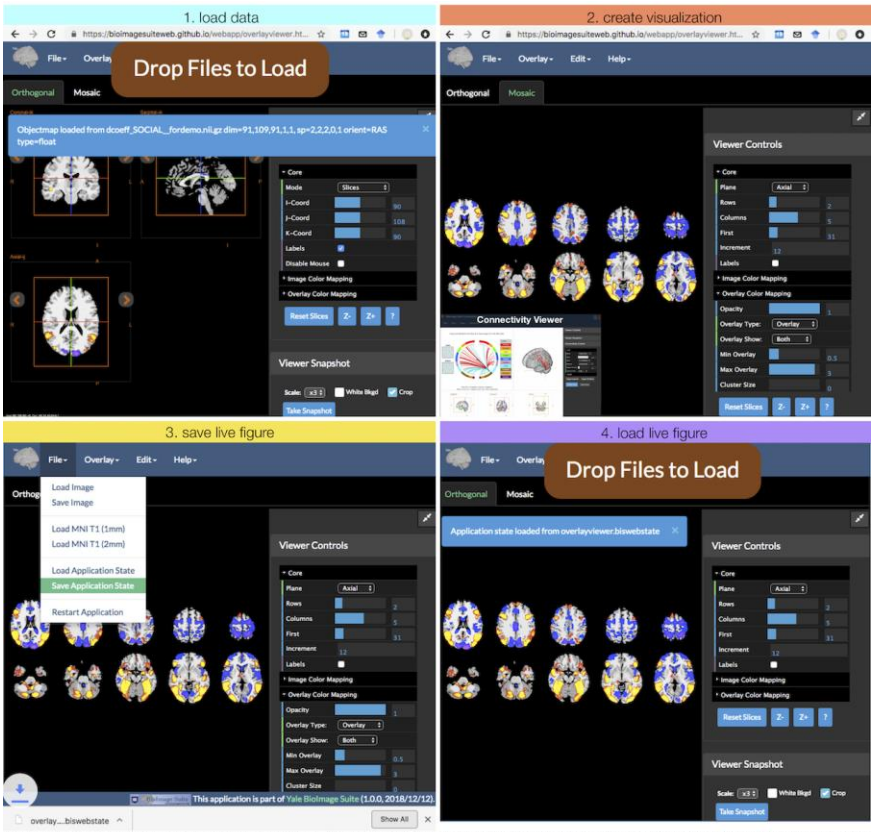

Figure 1. fMRI visualization and live figures in BISWeb. These screenshots demonstrate a typical process of fMRI image visualization in the Overlay Viewer application, resulting in a live figure that can be shared with a recipient (e.g., a collaborator). This example workflow demonstrates: (1) loading structural and overlay data, (2) creating a visualization of mosaic slices (inset: Connectivity Viewer application showing circle and glass brain plot), (3) saving the live figure, and (5) loading the live figure. Loading the live figure restores the full application state so that the user can continue where they left off, or a collaborator can adjust the figure.

Disclosures: S. Noble: None. **Z. Saltzman:** None. **C. Lacadie:** None. **H. Garbus:** None. **J. Onofrey:** None. **X. Papademetris:** None. **D. Scheinost:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.08/DD41

Topic: I.07. Data Analysis and Statistics

Title: Cloud-enabled massively parallel structural and functional MRI preprocessing pipeline

Authors: *H. GONZALEZ, M. E. KOLLADA, M. S. MELLEM, Y. LIU, O. RODRIGUEZ, P. AHAMMAD;
Blackthorn Therapeut., San Francisco, CA

Abstract: The preprocessing of structural and functional MRI scans is a computationally-intensive operation, typically taking several hours per subject. This results in prohibitively long waits between MRI data acquisition and analysis, particularly in large datasets with many hundreds of subjects, when computation is performed using traditional infrastructure such as workstation units. Here we present our cloud-enabled massively-parallel MRI preprocessing pipeline, integrated from technologies widely used in the scientific community and capable of preprocessing an average of more than 150 scans per day.
We built a preprocessing pipeline, using the FreeSurfer and AFNI software suites, that takes raw structural and resting-state functional MRI data and outputs parcelated and voxel-level time series as well as functional connectivity matrices. Internally, we perform the following steps to preprocess the raw data: structural preprocessing, despiking, motion correction, skull-stripping, co-registration between structural and functional images, spatial smoothing, normalization by mean signal, nuisance signal regression, and normalization to the MNI space. Our pipeline follows the Brain Imaging Data Structure (BIDS) standard and was designed from the ground up to be used as a cloud service, retrieving and storing files on demand in AWS S3 and executing in Docker containers that require minimal support. Our pipeline is also compatible with AWS Batch, enabling us to preprocess complete large-scale datasets in parallel using a cloud-based cluster environment.
We tested our pipeline by preprocessing the resting-state scans from the following datasets: ABIDE I, CNP, and EMBARC. Our pipeline preprocessed the CNP dataset in 43 hours (N=251, 5.8 subjects/hour), the EMBARC dataset in 42 hours (N=326, 7.7 subjects/hour), and the ABIDE I dataset in 80 hours (N=1056, 13.2 subjects/hour).Our pipeline code was executed in "c5" AWS EC2 computers with 8GB of RAM per container. These results were obtained using up to 1300 concurrent AWS EC2 vCPUs.
Compared to traditional local non-parallel computation, our MRI preprocessing pipeline opens the door to big data analysis of MRI datasets. We have shown that by bringing state-of-the-art technology to neuro-imaging analysis, we can create a flexible on-demand high-performance computing infrastructure with minimal offline footprint, and potential for reducing long-term cost. Our approach significantly reduced the end-to-end preprocessing time for complete MRI datasets, and holds promise in enabling scientists to study the effect and sensitivity of parameter changes across datasets with many thousands of subjects.

Disclosures: **H. Gonzalez:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. **M.E. Kollada:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. **M.S. Mellem:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. **Y. Liu:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. **O.**

Rodriguez: A. Employment/Salary (full or part-time):; BlackThorn Therapeutics. **P. Ahammad:** A. Employment/Salary (full or part-time):; BlackThorn Therapeutics.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.09/DD42

Topic: I.07. Data Analysis and Statistics

Support: DFG SFB 1134/A03

Title: AISuite: A Python tool for morphometrical analysis

Authors: *J. ROOS, M. ENGELHARDT;
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Abstract: Morphometrical analysis of data obtained by immunofluorescent stainings after high resolution microscopic imaging has played a key role in our understanding of subcellular neuronal domains, such as the axon initial segment (AIS) and its plasticity. So far, morphometrical analysis of AIS parameters, particularly length, distance from soma or diameter has been accomplished with software tools such as Neurolucida or ImageJ and self-written macros or simply measuring “by hand” in the software supplied by the microscope manufacturer. These numerous applications have led to data acquisition with a varying degree of scientific precision. In today’s landscape of proprietary and barely interoperable software, it has become evident that there is a need for a solution that is open and easy to use. AISuite was designed to fill this gap. After evaluating the state of analytical tools in the literature, we developed a strategy for an open-source, user-flow centric and expandable application. Python - a potent scientific programming language - was selected as the basis of the software suite, integrating performant compiled libraries such as OpenCV, NumPy and the extensive ImageJ libraries. Regarding data handling, and due to the limitations of the proprietary landscape of microscope manufacturers, AISuite provides an initial conversion step of the raw microscopic data into NumPy arrays through the ImageJ Bioformats reader. This step also saves all of the OMEXML compliant metadata of the acquisition process into a hierarchical data format file (HDF5), which contains all future alterations and data acquisition within the same experiment. The HDF file format has been selected for its standardized and asynchronous accessibility from different programming languages. Accurate 3D to 2D projections are integrated with an implementation of a sliced Maximum Intensity Projection, which can be adjusted to the best fitting limits. However, AISuite is also undergoing further optimization of data analysis in 3D confocal stack data, which would further limit pre-analysis data manipulation. AISuite allows for different ROI selection modules utilizing a line drawing tool, which is supported by a graphical tablet and pen. Throughout the development, a constant feedback and feature request cycle was established

among members of the lab as well as others from the scientific community, providing various data sets to test and validate the software. Here, we present an open source, freely available solution providing a standardized workflow to analyze various morphological features in neurons and other cells. Additionally, we continue to develop the program for web-based applications.

Disclosures: J. Roos: None. **M. Engelhardt:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.10/DD43

Topic: I.07. Data Analysis and Statistics

Support: HSE Basic Research Program
The Russian Academic Excellence Project '5-100'

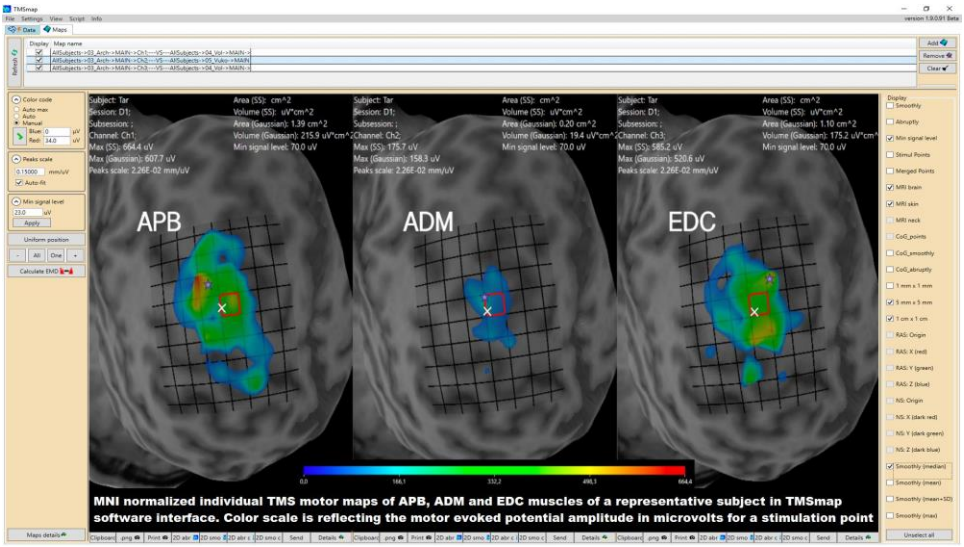
Title: TMSmap software for analysis of transcranial magnetic stimulation mapping results - Demonstration of the new features

Authors: *P. NOVIKOV[1], M. NAZAROVA[1,3], K. KOZLOVA[1], E. IVANINA[2], V. NIKULIN[1,4,5];
[1]Ctr. for Cognition and Decision Making, Inst. for Cognitive Neurosci., [2]Dept. of Psychology, HSE Univ., Moscow, Russian Federation; [3]Dept. of Neurorehabilitation, Federal Ctr. for Cerebrovascular Pathology and Stroke, The Ministry of Healthcare of the Russian Federation, Federal State Budget Inst., Moscow, Russian Federation; [4]Dept. of Neurol., Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [5]Neurophysics Group, Dept. of Neurol., Campus Benjamin Franklin, Charité—Universitätsmedizin Berlin, Berlin, Germany

Abstract: Here we present a new version of free software for standardising quantitative analysis of the data obtained with transcranial magnetic stimulation (TMS) mapping procedure - TMSmap (a previous version is described here (Novikov et al., 2018), http://tmsmap.ru/). The program allows estimating standard TMS map parameters such as areas and volumes, locations of the hotspots and centres of gravity of the cortical representations, as well as excitability profiles of the cortical representations, the overlap between the cortical representations and other user-defined parameters. New version of the program has an option for co-registering TMS mapping data to Montreal Neurological Institute (MNI) space (Figure 1) and thus allowing group comparison of the TMS mapping results. For convenient group analysis it is possible to load data and compare TMS maps automatically using a predefined script. New version of TMSmap also includes the possibility to analyse only stimulation points corresponding to a specific brain structure visible on MRI image, for example analysing only the map based on the stimuli applied in the vicinity of the central sulcus.

Input data for the software includes the coordinates of the coil position or calculated locations of the induced electric field (depending on the neuronavigation system), structural MRI data and a response at each point of stimulation (motor evoked potentials, behavioural response etc.). TMSmap was developed for the versatile assessment and comparison of the cortical maps following different experimental interventions including but not limited to longitudinal studies (e.g., studying of cortical reorganization during rehabilitation after stroke).

References:
Novikov PA, Nazarova MA and Nikulin VV (2018) TMSmap - Software for Quantitative Analysis of TMS Mapping Results. Front. Hum. Neurosci. 12:239. doi: 10.3389/fnhum.2018.00239



MNI normalized individual TMS motor maps of APB, ADM and EDC muscles of a representative subject in TMSmap software interface. Color scale is reflecting the motor evoked potential amplitude in microvolts for a stimulation point

Disclosures: **P. Novikov:** None. **M. Nazarova:** None. **K. Kozlova:** None. **E. Ivanina:** None. **V. Nikulin:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.11/DD44

Topic: I.07. Data Analysis and Statistics

Support: NSF SMA-1734795
NSF SMA-1734813

Title: Cell detection and segmentation via persistent homology

Authors: *U. KILIC[1], M. VAIANA[2], E. M. GOLDBERG[3], S. E. MULDOON[4];
[1]Dept. of Mathematics, Univ. At Buffalo, SUNY, Buffalo, NY; [2]Mathematics, Univ. At Buffalo, Buffalo, NY; [3]Neurol., The Children's Hosp. of Philadelphia, Philadelphia, PA; [4]Univ. at Buffalo, SUNY, Buffalo, NY

Abstract: Analyzing neuroimaging data at the cellular level often involves the tedious task of localizing and/or segmenting cells in images. Although automated cell detection methods exist and can be utilized for certain types of data, in noisy images, cell localization can prove difficult and manual or semi-manual methods are often employed. Here, we present a new algorithm that draws from mathematical tools in applied topology, specifically persistent homology, to perform cell localization and segmentation in neuroimaging data. Importantly, this method is robust to small perturbations, and therefore advantageous for use in images with small amounts of noise. The method can be applied to images in which cells appear either as filled regions (using 0-dimensional homology) or as donut-shaped objects (using 1-dimensional homology). To verify the performance of the technique to detect filled regions, we apply the algorithm to a large set of images drawn from the 2018 KAGGLE Data Bowl: Nuclei Detection Competition and achieve high accuracy in localizing cells. We then provide examples of how 1-dimensional homology can be used to detect and segment neurons in calcium imaging data or to perform myelin segmentation in microscopy images.

Disclosures: U. Kilic: None. **M. Vaiana:** None. **E.M. Goldberg:** None. **S.E. Muldoon:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.12/DD45

Topic: I.07. Data Analysis and Statistics

Support: NIMH Grant R44-MH105091

Title: Advanced machine learning in Cellairus: The next generation of unbiased stereology

Authors: *W. D. PACK[1], N. ROUSSEL[1], A. D. LEDUC[1], B. S. EASTWOOD[1], C. R. BATES[1], H. L. KESSLER[1], J. MCMULLEN[1], S. J. TAPPAN[1], P. J. ANGSTMAN[1], F. DU[2], M. LIU[2], J. R. GLASER[1];
[1]MBF Biosci., Williston, VT; [2]FD NeuroTechnologies, Inc., Columbia, MD

Abstract: With the advent of Cellairus, automated stereology has risen to the forefront of object quantification research by leveraging artificial intelligence to reduce manual cell marking. The manual aspects of stereology have been a barrier to widespread utilization of unbiased stereology. Cellairus dramatically accelerates stereological cell counting through the use of

machine learning to replicate expert observer judgments of cell location and size. Once the machine learning algorithms are trained, Cellairus identifies cells in 3D volumes throughout 3D brain regions using the same observer criteria as a human expert. Additionally, automation avoids user fatigue and subjectivity by consistently applying the same cell counting criteria throughout the brain. The unbiased results can be audited and reviewed for every counting frame site. Cellairus makes stereology easier, more robust, and faster. In Cellairus, 3D image volumes are analyzed using the Optical Fractionator probe using 3D detection methods to ensure accurate cell detection and unbiased population estimates. Cellairus is trained to differentiate between cells and non-cell objects. Even dense populations of cells are counted correctly. Cellairus uses a patent pending technique to perform true 3D stereological analysis. In contrast, other 'automated stereology' counting technologies utilize methodical shortcuts, e.g., analyzing 2D images collapsed from 3D volumes, that reduce accuracy and introduce bias. In this study, we validated the cell counts from the Caudate-Putamen in mouse brains by comparing automated stereology results with ground-truth data collected by manual stereology. Coronal brain sections were prepared with two fluorescent labels, DAPI and NeuN. Manual and automated stereology were performed for both wide-field fluorescence and scanning laser confocal microscopy in order to assess the performance of Cellairus across multiple imaging technologies. Population estimates, coefficients of error, false positive, false negative, and true positive detection rates were quantified and compared between cell counting methods and imaging modalities.

Disclosures: **W.D. Pack:** A. Employment/Salary (full or part-time):; MBF Bioscience. **N. Roussel:** A. Employment/Salary (full or part-time):; MBF Bioscience. **A.D. LeDuc:** A. Employment/Salary (full or part-time):; MBF Bioscience. **B.S. Eastwood:** A. Employment/Salary (full or part-time):; MBF Bioscience. **C.R. Bates:** A. Employment/Salary (full or part-time):; MBF Bioscience. **H.L. Kessler:** A. Employment/Salary (full or part-time):; MBF Bioscience. **J. McMullen:** A. Employment/Salary (full or part-time):; MBF Bioscience. **S.J. Tappan:** A. Employment/Salary (full or part-time):; MBF Bioscience. **P.J. Angstman:** A. Employment/Salary (full or part-time):; MBF Bioscience. **F. Du:** A. Employment/Salary (full or part-time):; FD NeuroTechnologies, Inc. **M. Liu:** A. Employment/Salary (full or part-time):; FD NeuroTechnologies, Inc. **J.R. Glaser:** A. Employment/Salary (full or part-time):; MBF Bioscience.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.13/DD46

Topic: I.07. Data Analysis and Statistics

Support: MH114678

Title: Data interface and apps for systems neurophysiology and imaging

Authors: D. GARCIA MURILLO[1], Z. WANG[1], O. ROGOVIN[2], S. CHEN[2], O. PAPAEMMANOUIL[1], *S. D. VAN HOOSER[2];
[1]Computer Sci., [2]Biol., Brandeis Univ., Waltham, MA

Abstract: Technology for recording from the brain is developing at a breakneck pace. But the digital integration of data acquired from different recording technologies is an impediment to the rapid adoption of these technologies across labs, and also makes analysis by interested 3rd parties, such as theorists, difficult. This lack of integration is a major barrier to scientific inquiry, as labs cannot easily analyze each other's data. Funding agencies are increasingly concerned with reproducibility, rigor, and distribution of data, even though there is no generally accepted "library" process for sharing these data. Common data interfaces would facilitate the development of common analysis code, leading to an increase in code testing and robustness, and an increase in reproducibility and rigor.
We present a data interface standard for neurophysiological and imaging data. The standard is not a file format but rather is a systematic means of specifying and accessing data used in the neurosciences, including voltage waveforms, imaging data, spike times of neurons, and intensity values in regions-of-interest within imaging data. The data interface standard can be implemented in any programming language. On the one hand, the interface includes tools for reading files from several Multifunction Data Acquisition Devices, 2-photon microscopes, and stimulus devices, and tools for handling the fact that different investigators often organize their data differently on disk. On the other hand, the interface contains a powerful extendible database so that the results of analyses and extracted quantities can be stored and queried. These features allow for an eco-system of best-of-breed "apps" to be developed or converted from existing open source tools, that store standardized results in the database.
The long-range goal of the project is to enable experimentalists, theorists, and even amateurs to exchange data easily and to begin meaningful analysis within the hour of download. This has the capability to transform neuroscience into a discipline more like astronomy, where data is widely shared and many theorists and amateurs contribute to new discoveries.

Disclosures: D. Garcia Murillo: None. **Z. Wang:** None. **O. Rogovin:** None. **S. Chen:** None. **O. Papaemmanouil:** None. **S.D. Van Hooser:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.14/DD47

Topic: I.07. Data Analysis and Statistics

Support: VA RR&D RX002783

Title: ANTs-based pipeline for preprocessing structural neuroimaging data from stroke patients

Authors: *H. HECTOR[1], I. PAPPAS[3], K. HAWS[4], B. CURRAN[5], A. S. KAYSER[2], M. D'ESPOSITO[3];
[2]Neurol., [1]Univ. of California, San Francisco, San Francisco, CA; [3]Helen Wills Neurosci. Inst., Univ. of California, Berkeley, Berkeley, CA; [5]Res., [4]VA Northern California Hlth. Care Syst., Martinez, CA

Abstract: Spatial normalization is a prerequisite to group-level analysis of neuroimaging data. Normalization transforms MR images of subjects' brains to a standard template, and thereby facilitates inter-subject comparisons. Standard normalization techniques, however, perform best on scans from healthy subjects and may perform poorly on scans from subjects with brain lesions.
Current methods for spatial normalization of MR images of brains with lesions include those that perform normalization through a cost-function that excludes the lesioned area as defined by a manually drawn "lesion mask" (Brett et al., 2001), and those that use tissue probability maps to perform normalization and segmentation simultaneously via "unified segmentation" (Ashburner and Friston, 2005). Despite their widespread use, these methods haves not been validated.
We offer a spatial normalization method tailored to MR images of brains with lesions using Advanced Normalization Tools ("ANTs") (Avants et al., 2011).
Specifically, we (1) create a group-level template and its corresponding prior probability images. The template is constructed using an iterative approach by tuning the ANTs pipeline to our stroke data. As each structural image is registered to the template, a new template that minimizes the diffeomorphisms between the template and the individual structural image is created. The process converges until it meets a tolerance criterion (Avants et al., 2010). (2) We perform a rigid transformation of each subject's structural image to the template, and (3) apply ANTs' cross-sectional cortical thickness pipeline (Tustison et al., 2016) to each structural image using the group template and its priors as input. (4) We normalize the extracted brain images to the MNI template using the nonlinear SyN registration method and a lesion mask for cost-function masking (Avants et al., 2011). This creates a group-specific template that reduces the cost of directly mapping the lesioned brains to MNI space.
We collected structural MRI data from patients with brain lesions following a stroke (160 slices, slice thickness 1 mm, TR = 2300 ms, TE = 2.98 ms, FA = 9°, matrix 256 × 230, field of view 256 mm x 230 mm). Lesion masks were drawn manually and approved by two board-certified neurologists (AK, MD). We assessed the quality of our method by calculating a normalized mutual information score between the normalized lesioned brains and the MNI template. Our method achieved higher normalized mutual information than the unified segmentation and cost-function masking methods. We propose that our preprocessing framework yields the most accurate spatial normalization of MR images from subjects with brain lesions.

Disclosures: H. Hector: None. **I. Pappas:** None. **K. Haws:** None. **B. Curran:** None. **A.S. Kayser:** None. **M. D'Esposito:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.15/DD48

Topic: I.07. Data Analysis and Statistics

Support: U19NS107464

Title: Brain platform: A step towards standardized analysis of neuroimaging data

Authors: *S. AGHAYEE[1], Z. BOWEN[2], G. MAGNUSSON[4], M. DIEP[4], M. LINDVALL[5], A. PORTER[5], W. LOSERT[3];
[1]Univ. of Maryland, Col. Park, College Park, MD; [3]Col. of Computer Mathematical and Natural Sci., [2]Univ. of Maryland, College Park, MD; [4]Fraunhofer USA, Riverdale, MD; [5]Fraunhofer, Riverdale, MD

Abstract: Two photon calcium imaging has allowed for recording the activity of large populations of neurons simultaneously at single cell resolution. Over the years many analysis pipelines have been developed for extraction and inference of neuronal activity from neuroimaging data. However, a standardized data collection and analysis platform is still lacking in the field. Here we showcase the BRAIN platform that aims to act as a framework for neuroscience researchers to collaborate on reproducible experiments and perform their research in a more efficient way. The BRAIN platform will serve as a common platform for researchers to share algorithms, workflows, and data; enabling them to easily reproduce experiments and rapidly explore new ideas. Over time we expect the platform to assemble a large crowd sourced library of software packages and toolsets. Researchers will be capable of creating new workflows by chaining these software packages together. The NWB data format will be used to unify the difference in data inputs and formats between the lab instruments and software packages. The current iteration of the BRAIN platform has a few algorithms for the most common calcium imaging analysis operations such as motion correction, cell registration, signal extraction, and spike inference. The algorithms can be configured and arranged to form an image analysis pipeline. These algorithms come from open source packages such as Suite2p, and some provided by researchers at University of Maryland. Moving forward we plan to allow users to integrate their own software packages and toolsets across different data sources and programming languages.

Disclosures: S. Aghayee: None. **Z. Bowen:** None. **G. Magnusson:** None. **M. Diep:** None. **M. Lindvall:** None. **A. Porter:** None. **W. Losert:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.16/DD49

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R01MG111429
NIH Grant R41MH113252
NIH Grant RF1MG117053
NIH Grant R01NS091236

Title: Cost effective open-source platform for the physiological data collection simultaneously with fMRI

Authors: P. T. SUMMERS[1], *S.-H. LEE[2], Y.-Y. I. SHIH[2];
[1]Biomed. Engin., [2]Dept. of Neurol., The Univ. Of North Carolina At Chapel Hill, Chapel Hill, NC

Abstract: In fMRI research, multiple devices are used to monitor resting state physiological conditions, including heart rate, body temperature, SpO_2, and $EtCO_2$. These conditions are known to contribute as nuisance noise, and many attempts have been made to find the correlation of these signals with Blood Oxygen Level-Dependent (BOLD) signal to regress out these nuisance components from the image data. There has yet to be a cost-effective platform allowing to collect physiological data from multiple devices facilitating efficient for synchronizing it with fMRI data. We designed a device integrating the open source platforms, Raspberry Pi and Arduino microcontrollers, to interface with measuring instruments to collect and store physiological data during MRI scans. The system implements Python and C++, enabling customization for different experimental setups and processing the signal. We used Arduino Uno as an analog-digital converter to deliver acquire analog signal at 9.6 kHz to the Raspberry Pi that is only allowing digital input though GPIO pins with a sample rate of 200 kHz. The trigger signal from the MRI scanner is used to synchronize these multi-modal data. The touchscreen monitor was used to couple with simplified Graphics User Interface (GUI) for easy interaction and monitoring of vitals. As a result, the Raspberry Pi and accessories can be bought from Adafruit for $180, and the Arduino Uno costs only $22, bringing the total cost of the final product can be around $200, which is highly cost-effective compared to the commercial platform. Also using the open source design enables each MRI group to optimize the system for their own needs. In conclusion, because our automated system is highly cost-effective and tunable, we expect our platform can be easily integrated into a wide variety of neuroscience MRI groups to collect physiological parameters concurrently with fMRI acquisition.

Disclosures: P.T. Summers: None. **S. Lee:** None. **Y.I. Shih:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.17/DD50

Topic: I.07. Data Analysis and Statistics

Title: A python package for quantitative classification and characterization of single neuron full morphology

Authors: *P. XIE[1], Y. WANG[1], L. LIU[2], Z. ZHOU[1], Y. YU[1], W. WAN[3], T. WANG[3], Q. WANG[1], L. QU[3], J. A. HARRIS[1], H. ZENG[1], H. PENG[1];
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Abstract: Single cell morphology is a key feature for the definition of neuronal types since the specification of neuroanatomy. However, the complete morphological data of single neurons including intact local and long-range axon arbors, has just become available in recent years. Such data has paved the way to understanding the projection pathways of axons, density of axon/dendrite clusters, patterns of arborization and so on. Global efforts have been made to generate single neuron morphology data at large scales and there is an urgent need for methodologies for quantitative data analysis. Here, a python package is implemented for the purpose of feature quantification, cell type classification/characterization and flexible visualization. The package is designed for facilitating the community for efficient data exploration, interpretation and integration. The major analysis pipeline takes CCF-registered reconstructions as the input and includes the following modules:
1) Feature quantification of:
a. Arbor lengths across brain regions, based on the annotation of CCFv3.
b. Morphological features (defined by the L-measurement) of the shape, size and location of the dendrites and axon terminals.
c. Projection paths (defined by brain regions) of major axon branches.
2) Similarity metrics and clustering analysis:
a. Features normalization and selection.
b. Similarity measured for each feature sets by graph-based algorithms.
c. Co-clustering analysis through random resampling.
d. Consensus between feature sets for cluster calls.
3) Cluster characterization:
a. Differential feature detection for cluster separation at different levels.
b. Correspondence between objective and subjective classification.
4) Visualization:
a. Dimension reduction by PCA, tSNE or UMAP.

b. Interactive plotting and flexible sample/feature selection.
c. Visualization of neuron structures in the CCF template with flexible options of samples, features, neurite types and views.

Disclosures: **P. Xie:** None. **Y. Wang:** None. **L. Liu:** None. **Z. Zhou:** None. **Y. Yu:** None. **W. Wan:** None. **T. Wang:** None. **Q. Wang:** None. **L. Qu:** None. **J.A. Harris:** None. **H. Zeng:** None. **H. Peng:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.18/DD51

Topic: I.07. Data Analysis and Statistics

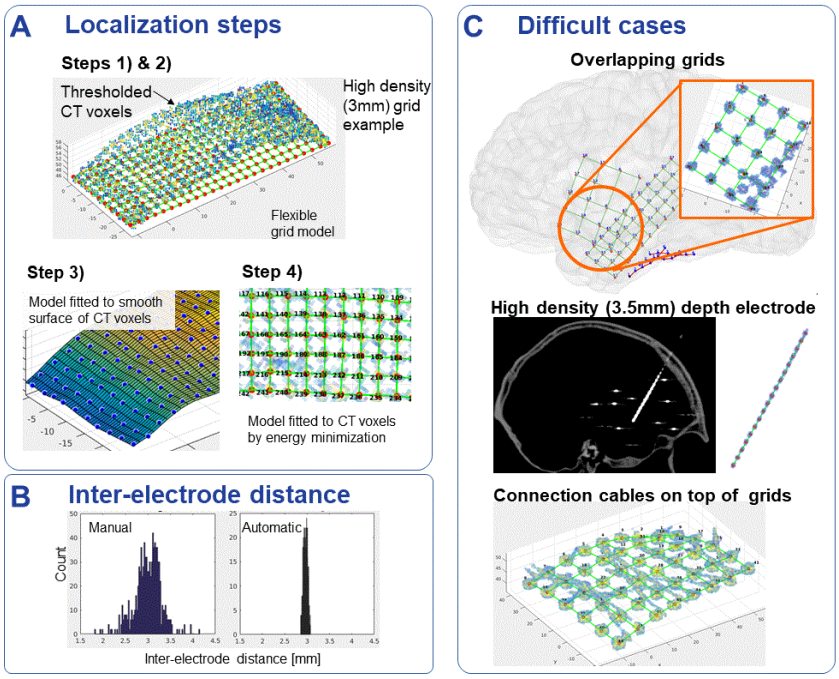
Support: NIH R37NS21135 and NIMH Silvio O. Conte Center 1PO MH109429-01
Research Council of Norway - grant number 240389/F20.

Title: A robust intracranial electrode localization algorithm

Authors: ***T. ENDESTAD**[1], A.-K. SOLBAKK[2], J. IVANOVIC[3], P. LARSSON[3], R. T. KNIGHT[4], A. O. BLENKMANN[1];
[1]Univ. of Oslo, Oslo, Norway; [2]Univ. of Oslo, Bekkestua, Norway; [3]Oslo Univ. Hosp., Oslo, Norway; [4]Univ. of California Berkeley, Berkeley, CA

Abstract: The accurate localization of electrodes in relationship to the brain's anatomy is the foundation of the spatial resolution of intracranial EEG recordings. However, in "difficult cases" the localization needs to be done manually since automatic methods often fail. This could be high density arrays up to 3 mm inter-electrode distance, overlapping electrodes, low resolution CT images, or connection cables ovelaying grids. Here, we present a new fully automatic method that models a flexible array of electrodes and fits it to the artifacts observed in post implantation CT images.
We evaluated data from 18 adult patients with drug resistant epilepsy implanted with depth electrodes and/or subdural grids (18 patients, 3261 electrodes). The localization results of the automatic method were compared to manual localization.
The main processing steps (Fig. 1 A) were:
1) Thresholding and selection of a cloud of CT voxels containing the electrode artifacts
2) Assembling a model of the grid (depth) array of electrodes
3) Fitting the model to a smooth surface (line) approximation of CT artifacts
4) Fitting the model to the cloud of voxels by minimizing the energy function
$E = -Ec + Et + Ed$
Ec is the gaussian weighted spatial correlation between the electrodes and the cloud of voxels. Et

penalizes the translation of electrodes, and Ed penalizes the deformation of a spring grid connecting the electrodes.By using this energy minimization approach, all electrodes are localized simultaneously instead of the usual individual localization, and therefore less sensitive to noise.
Automatic localization resulted to be more precise than manual selection, observed as a significant reduction of the inter-electrode distance variance (Fig. 1 B).
We provide a robust method for intracranial electrode localization that is applicable to “difficult cases” were previous automatic methods fail (Fig. 1 C).
The method was implemented in the open-source iElectrodes toolbox and is available to the research community (Blenkmann et al., 2017).



Disclosures: **T. Endestad:** None. **A. Solbakk:** None. **J. Ivanovic:** None. **P. Larsson:** None. **A.O. Blenkmann:** None. **R.T. Knight:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.19/DD52

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant NS100559

Title: An affordable and accurate tool to target subcortical structures in non-human primate

Authors: *S.-E. PARK[1], Z. LIANG[2], C.-A. N. GUTEKUNST[2], M. J. CONNOLLY[2], A. DEVERGNAS[3], R. E. GROSS[2];
[1]Georgia Inst. of Technol., Atlanta, GA; [2]Neurosurg., Emory Univ. Sch. of Med., Atlanta, GA; [3]Yerkes Natl. Primate Res. Ctr., Atlanta, GA

Abstract: Despite great improvements in stereotactic navigation systems for human neurosurgery, most of the non-human primate (NHP) neurosurgeries are still planned using standard 2D brain atlases. When only relying on brain atlases, variance between NHP subjects can cause inaccurate implantation of electrodes and chambers. We developed a novel tool for stereotactic neurosurgical planning for chronic implantation of electrodes or chambers as well as for visualization of the recording trajectory after implantation. We describe here the use of this tool in a post-surgery condition for visualizing different structures of interest that could be reached through a chronic recording chamber. An MRI compatible chronic recording chamber aimed at the hippocampus was implanted using stereotaxic coordinates based on the Salim and Logothetis brain atlas. A post-surgical MRI scan was performed 1 week after the surgery. A grid loaded with vitamin E was inserted inside the chamber before the scan to visualize the center and possible angle of the chamber. The subcortical structures including subfields of basal ganglia and striatum as well as the hippocampus were identified by registering MRI to the pre-segmented 3D MRI brain atlas (Reveley-et-al, 2017) using FMRIB software library (FSL). The identified regions were then converted into the original coordinate space by using the inverse matrix of the registration. A predicted trajectory of the electrode at each location in the chamber was obtained using a homemade Matlab code. Electrophysiological single unit activities in the putamen, pallidum and the hippocampus were used to verify the predicted locations. LFP recordings further confirmed our prediction by showing the characteristic pattern of CA1 and CA3 in the hippocampus. This MRI-based tool provides accurate and fully automatized subject-specific identification of subcortical structures and is applicable for various designs of electrodes and chambers.

Disclosures: S. Park: None. **C.N. Gutekunst:** None. **M.J. Connolly:** None. **A. Devergnas:** None. **R.E. Gross:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.20/DD53

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant U24MH114827
Allen Institute for Brain Science

Title: Integration and web presentation of brain initiative cell census network data in the cell registry and allen brain explorer

Authors: *C. L. THOMPSON[1], L. NG[1], D. FENG[2], G. ACHARYA[1], T. S. MOLLENKOPF[3], T. GILLESPIE[4], G. HSU[1], S. MUFTI[1], F. D'ORAZI[2], A. E. BANDROWSKI[5], J. GEE[6], M. E. MARTONE[4], T. TICKLE[7], M. J. HAWRYLYCZ[8];
[1]Allen Inst. for Brain Sci., Seattle, WA; [2]Allen Inst. For Brain Sci., Seattle, WA; [3]Allen Inst., Seattle, WA; [4]Neurosci., [5]UCSD, La Jolla, CA; [6]Penn Image Computing and Sci. Lab., Univ. of Pennsylvania, Philadelphia, PA; [7]The Broad Inst. of MIT and Harvard, Cambridge, MA; [8]Modeling, Analysis, and Theory, Allen Inst. Brain Sci., Seattle, WA

Abstract: A detailed census of the morphological, electrophysiological, molecular and connectional properties of cell types in the brain is being performed by a consortium of laboratories as part of the Brain Initiative Cell Census Network (BICCN). The Allen Institute for Brain Science is supporting the goals of BICCN by providing a foundational community resource for integrated cell-centric data with an open-access 3D digital brain cell reference atlas with molecular, anatomical, and physiological annotations of brain cell types in mouse and in human. To facilitate integration of diverse datasets generated by >30 different laboratories, a new integrated data framework has been implemented and continues to be developed. This flexible and powerful backend data architecture utilizes a graph database, and implements a unified data schema with supporting ontologies across all teams, experiments and datasets. The public web interface accesses the data through an API and services to support search, and enacts FAIR principles (finable, accessible, interoperable, reusable). By integrating different data modalities into a cell-centric framework, we will support the BICCN objectives by producing a scientifically cogent cell census. Essential to this integration is the adoption of semantic standards, spatial registration of all data to common brain coordinate systems, and to the extent possible, the use of standardized data processing pipelines and normalization to enable cross-modality comparison and analysis. The currently available Cell Registry product provides a centralized and archival record of all cells profiled or imaging experiments generated by the BICCN. This registry enables search by experimental parameters and points to data archive locations for high resolution data and protocols. The next evolution of this portal will provide access to spatial anatomic features, genetic and transcriptomic features, analytical annotation, morphological and electrophysiological feature through an integrated online viewer.

Disclosures: C.L. Thompson: None. **L. Ng:** None. **D. Feng:** None. **G. Acharya:** None. **T.S. Mollenkopf:** None. **T. Gillespie:** None. **G. Hsu:** None. **S. Mufti:** None. **F. D'Orazi:** None. **A.E. Bandrowski:** None. **J. Gee:** None. **M.E. Martone:** None. **T. Tickle:** None. **M.J. Hawrylycz:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

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Program #/Poster #: 525.21/DD54

Topic: I.07. Data Analysis and Statistics

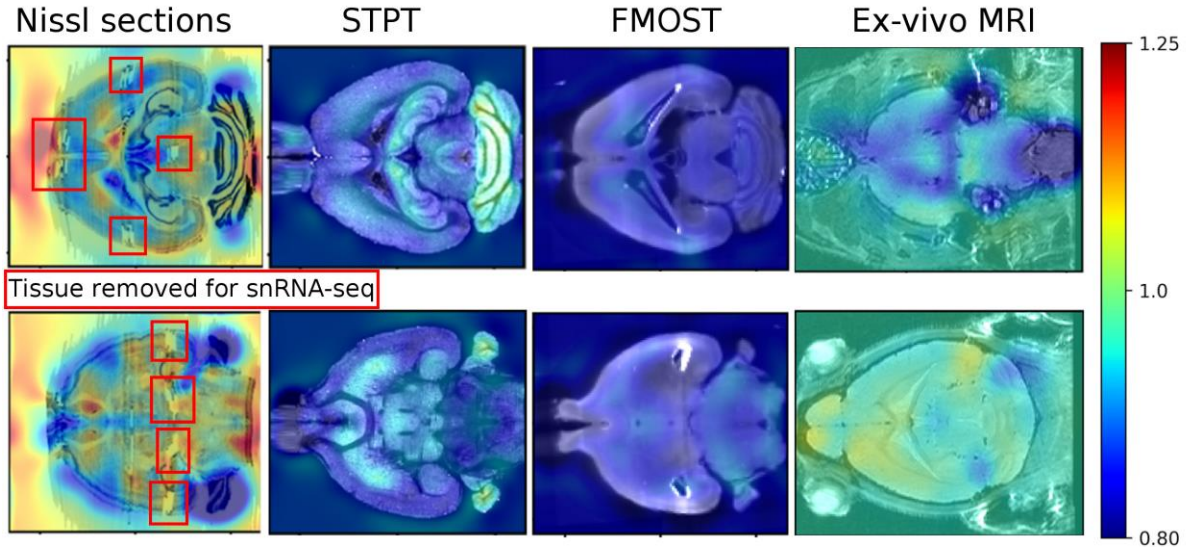
Support: NIH P41EB015909
NIH RO1NS086888
NIH R01EB020062
NIH R01NS102670
NIH U19AG033655
NIH R01MH105660
NIH U19MH114821

Title: Robust mapping of sectioned or 3D mouse brain images from multiple modalities using EM-LDDMM

Authors: *D. J. TWARD[1], B. C. LEE[1], X. LI[2], B. HUO[2], P. P. MITRA[2], M. MILLER[1]; [1]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD; [2]Cold Spring Harbor Lab., Cold Spring Harbor, NY

Abstract: The Brain Initiative Cell Census Network (BICCN) aims to obtain molecular, anatomical, and functional data across the mouse brain, mapped to a reference brain (CCF). Laboratories throughout the network use a host of imaging modalities to acquire data, including serial two photon tomography (STPT), fluorescence micro-optical sectioning tomography (FMOST), MRI, and light microscopy of Nissl stained tissue processed with tape transfer. These present variety in contrast, tissue loss or damage, artifacts, and 3D or 2D sectioning, making traditional registration approaches insufficient. The objective of this work is to build robust computational tools for mapping these datasets, and to quantify tissue distortion so comparisonsof cell/process densities can be made between modalities. We developed a statistical model for generating observed images from a 3D atlas, including 3D changes in shape and pose, optional 2D sectioning and distortion, changes in image contrast and color, and presence of artifacts and damaged or missing tissue. An Expectation Maximization (EM) algorithm was employed to calculate penalized maximum likelihood estimates of unknown transformations, built using the Large Deformation Diffeomorphic Metric Mapping (LDDMM) framework. This method, named EM-LDDMM, results in estimates that are robust to imaging variability.From the determinant of Jacobian of mappings we computed median linear scale change for each modality and found that two STPT brains are smaller by 7% and 5% relative to the CCF, FMOST smaller by 16%, and Nissl larger by 2%. Examining in vivo to ex vivo MRI of the same specimen showed in 4% shrinkage due to fixation. The figure shows two axial slices of these modalities,

aligned to the CCF, with linear scale change overlayed, and demonstrates that registration is robust to tissue removed for RNA sequencing and other variability.These mapping tools are being used to atlas-map data, made public via brainarchitecture.org, which will accelerate research throughout the BICCN and neuroscience community.



Disclosures: **D.J. Tward:** None. **B.C. Lee:** None. **X. Li:** None. **B. Huo:** None. **P.P. Mitra:** None. **M. Miller:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.22/DD55

Topic: I.07. Data Analysis and Statistics

Title: MorphoHub: An informatics platform for managing massive data production of neuron morphology

Authors: *S. JIANG[1], S. ZHAO[1], L. LIU[1], Z. ZHOU[3], Z. RUAN[1], Y. WANG[2], H. PENG[3]; [2]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, [1]Southeast Univ., Nanjing, China; [3]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Obtaining complete morphology of neurons from whole-brain imaging data is commonly accepted as a critical step towards the deciphering of the brain mechanisms. Whole-brain imaging techniques (such as fMOST) and computational tools for volume image visualization and annotation (such as Vaa3D [1], TeraFly [2], TeraVR [3]) have recently become more accessible, which make it possible for launching large-scale whole-brain neuron

reconstruction projects using industrial approaches. However, as the size of the reconstruction repositories for such a project typically grows at increasing rates, new requirements occur during the course not only in organizing and storing the morphological data, but in managing the reconstruction procedures, monitoring the overall progress, and many other aspects as well.
To address the above problems, we designed MorphoHub, an integrated informatics platform for data management, annotation workflow control and monitoring, data profiling and analysis, information visualization, etc. The informatics platform is built upon a hierarchical database model to organize both the imaging data and reconstruction data. The Relational Database Management System (RDBMS) is adopted to ensure data warehouse security and offer robust data backup/recovery. Most major functions of MorphoHub are implemented as services mounted on top of the RDBMS. The Annotation Service is used to transfer annotation data of different levels between the data server and the annotation workstation, with the guidance of a clearly defined working protocol. The Data Management Service generates tracking tables for reconstruction status and permits an administrator to edit the database. The Data Visualization Service displays the real-time states of the overall reconstruction project on a wall-mount big screen system, such as the morphology of newly reconstructed cells, the progress of individual brains, and the analysis of the neuron reconstructions.
We assembled a team of 20 annotators at SEU-Allen and some other collaborating research centers. With the help of MorphoHub, several remarkable results, e.g. producing ~1,000 neuron morphologies of mouse brains, was achieved in about one year time.
[1] Peng et al. "V3D enables real-time 3D visualization and quantitative analysis of large-scale biological image data sets." Nat biotech (2010).
[2] Bria et al. "TeraFly: real-time three-dimensional visualization and annotation of terabytes of multidimensional volumetric images." Nat meth (2016).
[3] Wang et al. "TeraVR Empowers Precise Reconstruction of Complete 3-D Neuronal Morphology in the Whole Brain." Biorxiv, https://doi.org/10.1101/621011 (2019).

Disclosures: **S. Jiang:** None. **S. Zhao:** None. **L. Liu:** None. **Z. Zhou:** None. **Z. Ruan:** None. **Y. Wang:** None. **H. Peng:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.23/DD56

Topic: I.07. Data Analysis and Statistics

Support: Southeast University Funding

Title: A working protocol for reconstruction of 3D single neuron morphology

Authors: *L. LIU[1], Z. ZHOU[3], Y. YU[3], L. YIN[1], Y. SONG[1], P. XIE[4], Y. WANG[2], Y. WANG[6], S. A. SORENSEN[4], J. A. HARRIS[3], H. ZENG[5], W. XIE[7], H. PENG[3];
[2]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, [1]Southeast Univ., Nanjing, China; [3]Allen Inst. For Brain Sci., Seattle, WA; [5]Structured Sci., [4]Allen Inst. for Brain Sci., Seattle, WA; [6]Allen Inst., Seattle, WA; [7]Inst. of Life Sciences, Southeast Univ., Jiangsu, China

Abstract: Normally extracted from microscopy imaging data, 3-D morphology is one of the most defining features for neurons. The process for obtaining morphology data is known as neuron reconstruction or neuron annotation, which is usually a nontrivial task especially for the cases of mammalian brains. Although promising automatic neuron reconstruction approaches emerged during recent years, manual efforts are nonetheless indispensable if precise and complete reconstructions are desired. Typically, the exhaustive reconstruction of full morphology from whole-mammalian brains could cost considerable time even for a team of experienced annotators. Thus, a methodology for accurate, efficient, scalable, organized, and manageable production of morphology data becomes a rising needed. In this work, we present a four-level protocol to systematically guide the neuron reconstruction process with clear standards. From lower to higher levels, the reconstruction criteria become stricter and the corresponding morphology data gets more refined with details. The easy-to-use protocol allows the combination of both automatic and manual procedures in a flexible order, and intuitively integrates several novel techniques including artificial intelligence and virtual reality. Based on such a protocol, a team of 20 annotators has smoothly reconstructed more than 700 neurons located in the thalamus, striatum, spiny claustrum, etc. of mouse brains. A large portion of the produced data have been released to the Brain Initiative Cell Census Network (BICCN).

Disclosures: L. Liu: None. **Z. Zhou:** None. **Y. Yu:** None. **L. Yin:** None. **Y. Song:** None. **P. Xie:** None. **Y. Wang:** None. **Y. Wang:** None. **S.A. Sorensen:** None. **J.A. Harris:** None. **H. Zeng:** None. **W. Xie:** None. **H. Peng:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.24/DD57

Topic: I.07. Data Analysis and Statistics

Title: Automatic multi-scale neuron refinement for whole mouse brain reconstruction

Authors: *Z. ZHOU[1], L. LIU[2], Y. WANG[4], Z. RUAN[2], H. PENG[1,3];
[1]Allen Inst. For Brain Sci., Seattle, WA; [3]Southeast Univ. – Allen Inst. Joint Ctr. for Neuron Morphology, [2]Southeast Univ., Nanjing, China; [4]Allen Inst., Seattle, WA

Abstract: Currently, reconstruction of 3-D full morphology of neurons at the whole-brain scale still requires intensive manual curation and annotation in trillions of image-voxels of a brain. Manual reconstructions are considered the gold standard to evaluate automated reconstructions and to generate training sets for machine learning based algorithms. To further explore more detailed morphologies, these whole brain reconstructions could also be used forneurites radius estimation, spine detection, and/or synaptic boutons counting. Therefore, generating high quality, biologically meaningful annotations is in great demand. Here, we introduce an automatic multi-scale refinement system for whole mouse brain neuron reconstruction. The proposed system evaluates the reconstruction at two different scales (low/high resolutions). At each scale, a graph-augmented deformable (GD) model based approach is used to automatically refine manual curated reconstructions. Combing Euclidean distance, pixel intensity along the path, and closeness to local centers of image intensity distribution, the GD model is designed to find the optimal path between two end points. We applied an automatic refinement approach on 500+ manual curated full morphology reconstructions. Our preliminary results show the refined reconstruction highly reflects the overall neuronal structures of manual reconstruction. At the same time, each segment in refined reconstruction is fine-tuned to better represent the original neuron structure.

Disclosures: **Z. Zhou:** None. **L. Liu:** None. **Y. Wang:** None. **Z. Ruan:** None. **H. Peng:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.25/DD58

Topic: I.07. Data Analysis and Statistics

Title: Single neuron morphology heterogeneity from a whole brain perspective

Authors: *L. MANUBENS-GIL[1], P. XIE[2], L. LIU[1], H. PENG[2,1];
[1]SEU-Allen Joint Ctr. for Neuron Morphology, Nanjing, China; [2]Allen Inst. for Brain Sciene, Seattle, WA

Abstract: Neuronal morphology is crucial for shaping brain connectivity. However, systematic analyses of the detailed morphology of full neurons from a whole brain perspective have not been possible due to a number of technical limitations. Using sub-micrometric resolution fMOST imaging of sparsely labeled neurons in whole mouse brains, the SEU-Allen Joint Center for Neuron Morphology started to release full neuron morphology reconstruction datasets at increasing pace. Here we reported an analysis of the dendritic and axonal trees of 95 neurons of a single mouse brain mainly distributed throughout the Thalamus and Caudoputamen. Our analysis shows a high degree of morphological variation within the studied brain regions, being higher in axons than dendrites. Neuron locations within the Thalamus and Caudoputamen brain areas do

not determine morphological types. However, thalamic neurons have smaller and less complex dendritic and axonal trees when located in lateral nuclei. Caudoputamen dendritic trees, conversely, show increased tree size and complexity for both posterior and lateral locations within the region. To assess whether neurons are segregated by their abilities to process and store information, we quantified the material cost, routing efficiency and connectivity repertoire of dendritic and axonal subtrees. Thalamus neurons have architectural traits maximizing storage capacity in both dendritic and axonal trees, while Caudoputamen neurons maximize routing efficiency. Moreover, thalamic dendrites seem to have segregated connectivity repertoire values in different nuclei. Thalamic neurons show distinct axonal projection patterns to the cortex, segregated in clusters throughout the antero-posterior axis that correspond to individual thalamic nuclei. Caudoputamen neurons mainly have local projections that do not vary depending on the location of the neurons within the region. Simulation of the axon potential propagation has shown diverse signal transmission dynamics among brain regions. Altogether our results show that (1) highly specific axonal projection patterns can follow discrete (Thalamus) or continuous (Caudoputamen) spatial distributions in distinc brain regions, and (2) currently defined anatomical parcellations account only for a small proportion of neuromorphological heterogeneity, which determines non-homogeneous information routing and storage capacities in brain circuits.

Disclosures: **L. Manubens-Gil:** None. **P. Xie:** None. **L. Liu:** None. **H. Peng:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.26/DD59

Topic: I.07. Data Analysis and Statistics

Support: NIH Grant R24-MH-114793
NSF Other Support OCI-1053575
NSF Other Support ACI-1445606

Title: The Brain Image Library

Authors: ***A. J. ROPELEWSKI**[1], A. WETZEL[1], G. HOOD[1], D. SIMMEL[1], K. BENNINGER[1], M. BRUCHEZ[2], A. WATSON[3], S. C. WATKINS[3];
[1]Pittsburgh Supercomputing Ctr., [2]Mol. Biosensor and Imaging Ctr., Carnegie Mellon Univ., Pittsburgh, PA; [3]Ctr. for Biologic Imaging, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: The Brain Image Library (BIL) is a unique resource of optical microscopy data for neuroscience investigators. The library is one of five NIH-designated repositories to receive BRAIN initiative data. Primary goals of the library are to preserve original research data from

brain studies that generate high-quality microscopy datasets at planar resolutions up to optical limits and sectional spacings from micron to hundreds of microns as dictated by their original experimental purpose. With single or multi-channel high-resolution data captures of mouse brains now exceeding 10 terabytes per specimen, these volumes have become increasingly difficult for research laboratories to store and exchange with remote sites. To make these datasets and data from larger mammalian species more widely available, the BIL provides a single site where data are stored once and then retrieved on-demand over nationwide high-speed networks for further research and academic uses. The library, now in its second year of operation, currently contains more than 750 contributed mouse full-brain volumetric datasets and is expected to grow to an aggregate store of 10 Petabytes over the next few years. The Brain Image Library also provides an extraordinary facility for both contributors and data users alike to interact with and select specific data subsets for further analyses from the BIL systems without requiring massive data downloads. This is achieved by BIL's support of a variety of remote-desktop mechanisms for remote visualization and data manipulations, including private virtual-machine environments capable of running commercial software and project-specific web portals. Allocations to high-performance computational resources are available for using PSC's large-scale Bridges computing system to directly interact with BIL data in-place using compute nodes with up to 12 Terabytes of shared memory, GPU nodes with P100 and V100 GPUs, and an NVIDIA DGX-2 to support high-bandwidth multi-GPU deep-learning applications. This design allows researchers to access these unique resources, bring their own software packages, and make use of software developed by other bio-imaging projects.

Disclosures: **A.J. Ropelewski:** None. **A. Wetzel:** None. **G. Hood:** None. **D. Simmel:** None. **K. Benninger:** None. **M. Bruchez:** None. **A. Watson:** None. **S.C. Watkins:** None.

Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.27/DD60

Topic: I.07. Data Analysis and Statistics

Title: Immersive visualization is a key enabler for precise whole-brain scale reconstruction of neurons

Authors: *Y. WANG[1,2,3,4], Q. LI[3], L. LIU[1,2], Z. ZHOU[5,2], Y. WANG[5], L. KONG[3], H. PENG[1,2,3,5];
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Abstract: Neuron morphology, the 3-D digital representation of neurons, substantially helps neuroscientists to explore the underlying functions and mechanisms of brains. As techniques for sparse labeling and whole-brain imaging are more accessible, it now becomes feasible to reconstruct complete neuron morphology from whole-mammalian brains. For a complete morphology, both dendritic trees and axonal arborizations are expected to be precisely captured. Moreover, the reconstruction should be performed in an efficient way to achieve high-throughput data production. These requirements call for a powerful neuron reconstruction software that offers intuitive visualization and interaction.

We developed TeraVR [1], an open source virtual reality (VR)-based neuron reconstruction system. The software was quickly adopted by SEU-Allen and several other collaborating research teams to help fulfilling their goal in producing thousands or even millions of complete neuron morphologies. Integrated in Vaa3D [2], TeraVR natively gains the ability of handling imaging data of terabyte-scales [3], and can be readily enhanced by a broad line of Vaa3D plug-ins. Ever since its first release, TeraVR is continually being updated by adding more useful functionalities for neuron reconstruction and improving the human-computer interfaces to further boost productivity. In the meantime, morphology data generated using TeraVR was analyzed quantitatively to find out what really the strengths of TeraVR are. Analysis results firmly support the notion that TeraVR is the right tool to seek for when imaging data with complicated, weak, and/or noisy signals is encountered. With TeraVR, neuron reconstruction can be performed at an accuracy that has never been achieved before.

Recently, a dataset containing the complete morphology of 500+ neurons generated by TeraVR has been released to the public through BRAIN BICCN. Such data are expected to benefit the community in several ways, e.g. serving as defining features for discriminating cell types, or being used as gold standards for developing machine intelligence-based automatic neuron reconstruction approaches.

[1] Wang, Yimin, et al. "TeraVR Empowers Precise Reconstruction of Complete 3-D Neuronal Morphology in the Whole Brain." *Biorxiv,* https://doi.org/10.1101/621011 (2019).

[2] Peng, Hanchuan, et al. "V3D enables real-time 3D visualization and quantitative analysis of large-scale biological image data sets." *Nat biotech* 28.4 (2010): 348-353.

[3] Bria, Alessandro, et al. "TeraFly: real-time three-dimensional visualization and annotation of terabytes of multidimensional volumetric images." *Nat meth* 13.3 (2016): 192-194.

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Poster

525. Software Tools: Imaging

Location: Hall A

Time: Tuesday, October 22, 2019, 8:00 AM - 12:00 PM

Program #/Poster #: 525.28/DD61

Topic: I.07. Data Analysis and Statistics

Title: Ultratracer2 on HPC for high-throughput neuron morphology reconstruction

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Abstract: Neuron reconstruction at the whole-brain level is essential to the understanding and characterization of the 3D morphology of neurons. To facilitate the effort of obtaining such valuable data, a widely used platform, Vaa3D (Peng, et al, *Nature Biotechnology*, 2010, *Nature Protocols*, 2014), has been developed with visualization, auto-tracing and annotation functionality. Specifically, Vaa3D has been used as a key platform to enable the global *BigNeuron* initiative (Peng, et al, *Neuron*, 2015) that has produced the largest known archive of neuron reconstructions with over 3 million constructions in 2015. Also, an *UltraTracer* framework (Peng, et al, *Nature Methods* 2017) was developed to provide a generalized framework to enable reconstructing neurons from virtually unlimited large image volume. However, for mammalian brains, practically whole-brain neuron reconstruction has not been done in large-scale. In this work, we present a new framework with Vaa3D-UltraTracer2 and high performance computing(HPC) cluster employment for high-throughput reconstruction of whole-brain neuron reconstruction. In addition to UltraTracer's approach of divide-and-conquer and capability of using any basic tracer, UltraTracer2 adopts DeepNeuron(Z. Zhou et al., *Brain informatics*, 2018) to deal with the heterogenous background situation common in whole-brain image and employs confidence scores to help the determination of tracing process. UltraTracer2 also provides evaluation scores for the output reconstructions, which helps annotators to prioritize ones with good quality and thus improve the efficiency of annotation. We implemented the UltraTracer2 framework on HPC cluster to gain further computational efficiency. For each whole-brain data, a list of soma locations of the neurons are put through the system with one single command which runs all Ultratracer2 jobs. These jobs are distributed on the cluster nodes and are ran in parallel with job management system, hence HPC implementation speeds up UltraTracer2 framework. In this way, the UltraTracer2 on HPC framework increases the throughput of neuron reconstruction on whole brain level and thus facilitates the on-going effort of enlarging the data set of whole-brain neuron morphology reconstruction.

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Poster

525. Software Tools: Imaging

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Program #/Poster #: 525.29/DD62

Topic: I.07. Data Analysis and Statistics

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Title: Multi modal neuroimaging visualization and analysis tool

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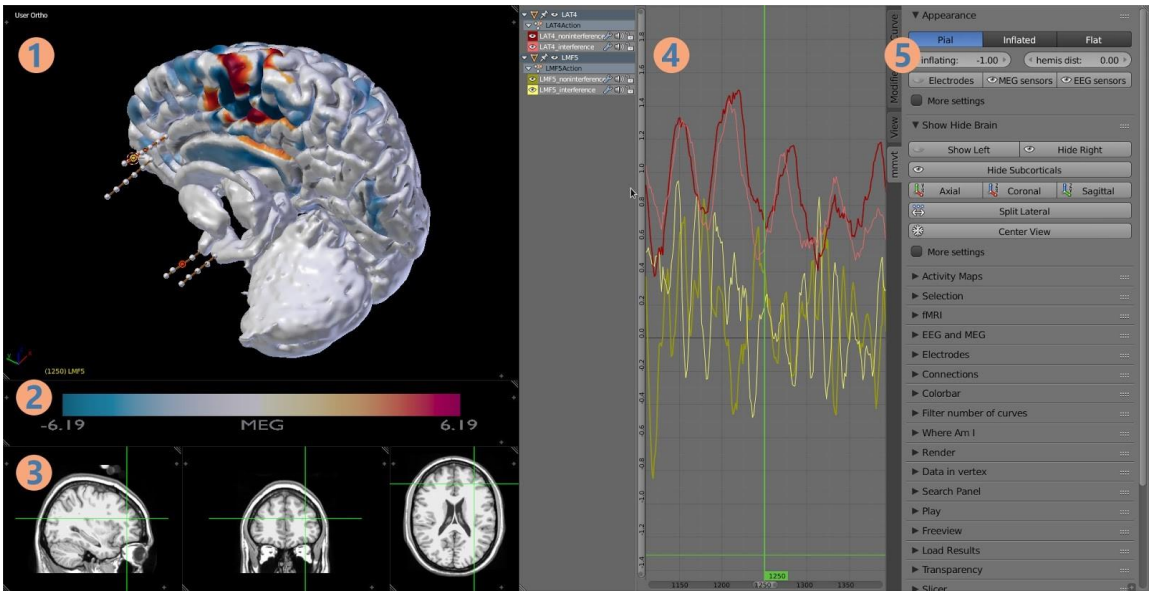
Abstract: Visualization and exploration of neuroimaging data are essential for the analysis of anatomical or functional images as well as statistical parametric maps. While two-dimensional orthogonal views of neuroimaging data are conventionally used to display activity and statistical analysis, real three dimensional (3D) depictions are useful for showing the spatial distribution of a functional network, as well as its temporal evolution. For these purposes, there is currently no open-source, 3D neuroimaging tool that can simultaneously visualize the following modalities: MRI, CT, EEG, MEG, fMRI, PET, and invasive electrodes (i.e., ECOG, depth electrodes, and DBS). Here we present the Multi-Modal Visualization Tool - MMVT (mmvt.org). This tool was built for researchers who wish to have a better understanding of their neuroimaging anatomical and functional data through simultaneous visualization of these existing imaging technologies. MMVT contains two separate modules: The first is an addon to the open-source, 3D-rendering program Blender. This addon is an interactive graphical interface which enables users to simultaneously visualize multi-modality functional and statistical data on the cortex and subcortical surfaces as well as the activity of invasive electrodes. This tool also enables highly accurate 3D visualization of neuroanatomy, including the location of invasive electrodes relative to brain structures. The second module includes stand-alone pre-processing full pipelines, from raw data to statistical maps. Each of the modules and module features can be integrated, separate from the tool, into existing data pipelines. This gives the tool a distinct advantage in both clinical and research domains as each has highly specialized visual and processing needs. MMVT leverages open-source programs and packages to build a comprehensive multimodal visualization tool for data visualization and exploration.



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Poster

525. Software Tools: Imaging

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Topic: I.07. Data Analysis and Statistics

Support: 10 animals were loaned for our research from the Vaika Foundation

Title: Cortical atlas of the canine brain

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Abstract: There is a need to identify and develop improved models for human neuroscience research. The dog has been bastioned as a potential unique model for comparative neuroscience research, an essential component of which is advanced neuroimaging. One limitation of the canine in this field is a lack of a brain atlas that includes a comprehensive myeloarchitectonic based cortical atlas for standardization and automation of cortical segmentation.

We created a canine brain atlas from isovolumetric T1-weighted MRI data generated in vivo from 30 neurologically healthy, mixed breed, mesaticephalic dogs. Data were preprocessed before registration and creation of a population template using Advanced Normalization Tools (ANTs). To assess the applicability of this template to other canine data sets with differing skull shapes an independent 3D T1-weighted MRI dataset of mesaticephalic, dolichocephalic, and brachycephalic neurologically healthy canines were recruited and, using non-linear registration, similarity metrics (mean normalized MI) were generated for each skull shape group. Delineation and parcellation of the cerebral cortex to create a cortical atlas was performed manually for each lobe in accordance with the myeloarchitectonic articles from Jerzy Kreiner. Region boundaries were established based on the myeloarchitectonic structure of the grey matter that is described in Kreiner's articles and depicted in images of cortical surfaces and transverse slices of the brain. In addition, subcortical structures were delineated using anatomic references and previous subcortical references.

The resulting atlas provides a mesaticephalic canine population template generated from healthy animals. When compared to other mesaticephalic dogs the similarity matrix of normalized MI had a mean value of -0.475 (st. dev. 0.0762) whereas for dolichocephalic and brachycephalic skull shape the normalized MI was increased to -0.449 (st. dev. 0) and -0.366 (st. dev. 0.0241) respectively. The myeloarchitectonic cortical parcellation resulted in generation of 108 cortical regions per hemisphere grouped into frontal, sensory-motor, perisylvian, parietal, cingulate and occipital lobar areas. Subcortical segmentations included olfactory lobe, hippocampus, cerebellum, amygdala, caudate, lateral and medial geniculate nuclei, and rostral and caudal colliculi.

This atlas provides intricate myeloarchitectonic based cortical segmentations which will function as a foundational tool for standardization and automation in future canine neuroimaging research.

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